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(54) Title: ANTIPICORNAVIRAL COMPOUNDS AND METHODS FOR THEIR USE AND PREPARATION

(57) Abstract

Picornaviral 3C protease inhibitors, obtainable by chemical synthesis, inhibit or block the biological activity of picornaviral 3C proteases. These compounds, as well as pharmaceutical compositions that contain these compounds, are suitable for treating patients or hosts infected with one or more picornaviruses. Several novel methods and intermediates can be used to prepare the novel picornaviral 3C protease inhibitors of the present invention.

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ANTIPICORNAVIRAL COMPOUNDS AND METHODS FOR THEIR USE AND PREPARATION

RELATED APPLICATION DATA

This application relates to U.S. Patent Application Nos. 08/825,331, filed March 28, 1997, and 08/850,398, filed May 2, 1997. Additionally, this application relates to U.S. Provisional Patent Application No. 60/046,204, filed May 12, 1997. Each of these U.S. patent applications relates to antipicornaviral compounds, compositions containing them, and methods for their production and use. Each of these applications also is entirely incorporated herein by reference. Additionally, this application relates to a concurrently filed U.S. patent application entitled "Antipicornaviral Compounds, Compositions Containing Them, and Methods for Their Use," U.S. Patent Appln. No. 08/991,282, filed in the names of inventors Peter S. Dragovich, Thomas J. Prins, and Ru Zhou. This concurrently filed application also is entirely incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention pertains to the discovery and use of new compounds that inhibit the enzymatic activity of picornaviral 3C proteases, specifically rhinovirus proteases ("RVPs"), as well as retard viral growth in cell culture.

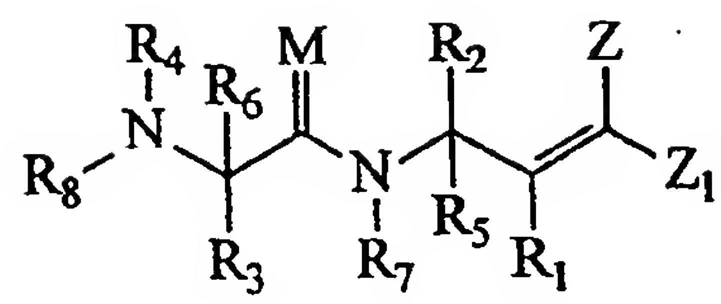
The picornaviruses are a family of tiny non-enveloped positive stranded RNA containing viruses that infect humans and other animals. These viruses include the human rhinoviruses, human polioviruses, human coxsackieviruses, human echoviruses, human and bovine enteroviruses, encephalomyocarditis viruses, menigovirus, foot and mouth viruses, hepatitis A virus, and others. The human rhinoviruses are a major cause of the common cold. To date, there are no effective therapies to cure the common cold, only treatments that relieve the symptoms.

Picornaviral infections may be treated by inhibiting the proteolytic 3C enzymes. These enzymes are required for the natural maturation of the picornaviruses. They are responsible for the autocatalytic cleavage of the genomic, large polyprotein into the essential viral proteins. Members of the 3C protease family are cysteine proteases, where the sulfhydryl group most often cleaves the glutamine-glycine amide bond. Inhibition of 3C proteases is believed to block proteolytic cleavage of the polyprotein, which in turn can retard the maturation and replication of the viruses by interfering with viral particle production. Therefore, inhibiting the processing of this cysteine protease with selective, small molecules that are specifically recognized, should represent an important and useful approach to treat or cure viral infections of this nature and, in particular, the common cold.

SUMMARY OF THE INVENTION

The present invention is directed to compounds that function as picornaviral 3C protease inhibitors, particularly those that have antiviral activity. It is further directed to the preparation and use of such 3C protease inhibitors. The Inventors demonstrate that the compounds of the present invention bind to rhinovirus 3C proteases and preferably have antiviral cell culture activity. The enzymatic inhibition assays used reveal that these compounds can bind irreversibly, and the cell culture assays demonstrate that these compounds can possess antiviral activity.

The present invention is directed to compounds of the formula (I):



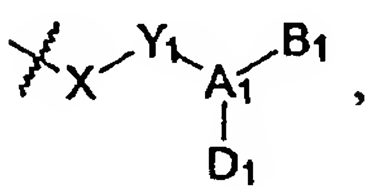
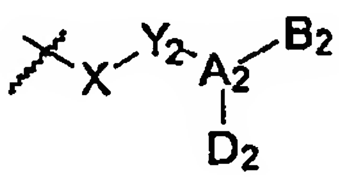
(I),

wherein:

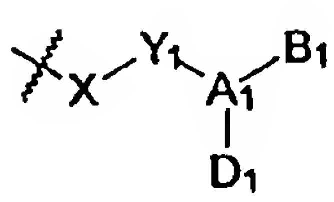
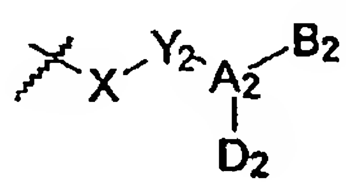
M is O or S;

R_1 is H, F, an alkyl group, OH, SH, or an O-alkyl group;

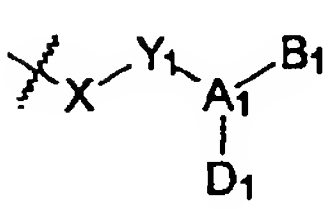
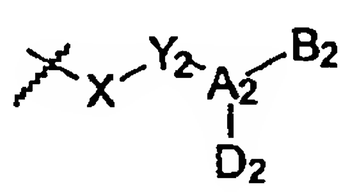
R_2 and R_5 are independently selected from H,

 ,  ,

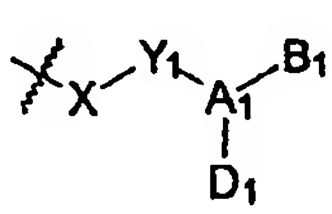
or an alkyl group, wherein the alkyl group is different from

 and  ,

with the proviso that at least one of R_2 or R_5 must be

 or  ,

and wherein, when R_2 or R_5 is



X is =CH or =CF and Y_1 is =CH or =CF,

or X and Y_1 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_1 is $-CH-$, $-CF-$, or -C(alkyl)-, where R_{10} and R_{11} independently are H, a halogen, or an alkyl

group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_1 is $-O-$, $-S-$, $-NR_{12}-$, $-C(R_{13})(R_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR_{13}R_{14})-$,

wherein R_{12} is H or alkyl, and R_{13} and R_{14} independently are H, F, or an alkyl group, or, together with the atoms to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

A_1 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_1 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and

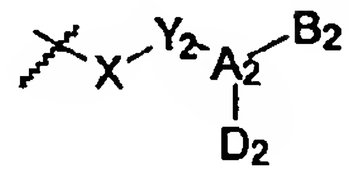
B_1 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N;

and further wherein, when R_2 or R_5 is



X is =CH or =CF and Y_2 is =C, =CH or =CF,

or X and Y_2 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_2 is $-CH-$, $-CF-$, or $-C(alkyl)-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_2 is $-O-$, $-S-$, $-N(R'_{12})-$, $-C(R'_{13})(R'_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR'_{13}R'_{14})-$,

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR'_{13}$, $-NR'_{13}R'_{14}$, $-C(O)-R'_{13}$, $-SO_2R'_{13}$, or $-C(S)R'_{13}$, and R'_{13} and R'_{14} independently are H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

A_2 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and

B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and further wherein any combination of Y_2, A_2, B_2, and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

R_3 and R_6 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{17}$, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or, R_3 and R_6, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

R_4 is any suitable organic moiety, or R_4 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

R_7 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or R_7 together with R_3 or R_6 and the atoms to which they are attached form a heterocycloalkyl group;

R_8 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-NR_{29}R_{30}$, $-OR_{29}$, or $-C(O)R_{29}$,

wherein R_{29} and R_{30} each independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

or R_8 together with R_4 and the nitrogen atom to which they are attached form a heterocycloalkyl group or a heteroaryl group, or R_8 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

or Z_1, as defined above, together with R_1, as defined above, and the atoms to which Z_1 and R_1 are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z_1, both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

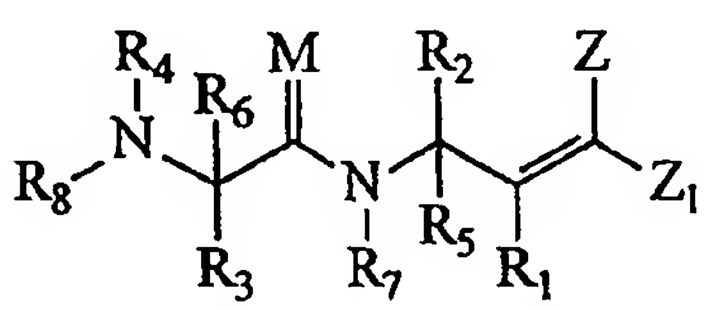
with the proviso that when R_7 is H, R_8 is a moiety other than H;

and pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof;

and wherein these compounds, pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

DETAILED DESCRIPTION OF THE INVENTION

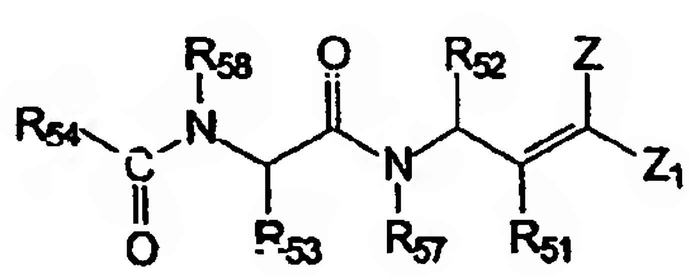
The present invention relates to compounds of the formula I



(I),

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, M, Z, and Z_1 are as defined above, and to the pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof, where these compounds, pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

The present invention preferably relates to compounds of the formula II:

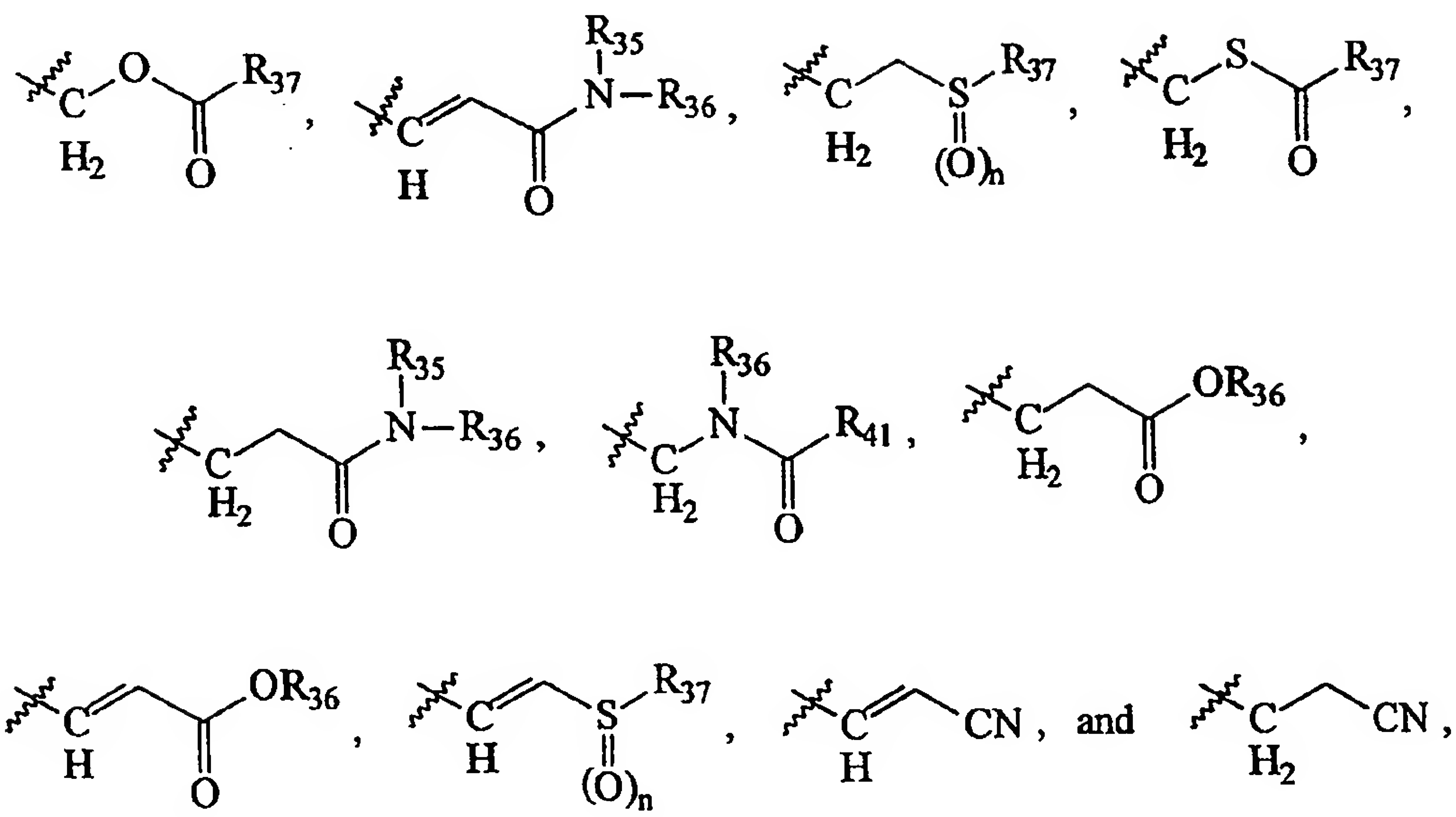


(II),

wherein:

R_{51} is H, F, or an alkyl group;

R_{52} is selected from one of the following moieties:



wherein:

R_{35} is H, an alkyl group, an aryl group, $-OR_{38}$, or $-NR_{38}R_{39}$,

wherein R_{38} and R_{39} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

R_{36} is H or an alkyl group,

or R_{35} and R_{36}, together with the nitrogen atom to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$, wherein R_{38} and R_{39} are as defined above;

R_{41} is H, an alkyl group, an aryl group, $-OR_{38}$, $-SR_{39}$, $-NR_{38}R_{39}$, $-NR_{40}NR_{38}R_{39}$, or

$-NR_{38}OR_{39}$, or R_{41} and R_{36}, together with the atom(s) to which they are attached, form a heterocycloalkyl group;

wherein R_{38} and R_{39} are as defined above, and R_{40} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

n is 0, 1 or 2;

R_{53} is H or an alkyl group;

R_{54} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl group, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group;

or R_{54} together with R_{58} and the nitrogen atom to which they are attached form a heterocycloalkyl group or a heteroaryl group;

R_{57} is H or an alkyl group;

R_{58} is H, an alkyl group, a cycloalkyl group, $-OR_{70}$, or $NR_{70}R_{71}$, wherein R_{70} and R_{71} are independently H or an alkyl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or

a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or wherein Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group;

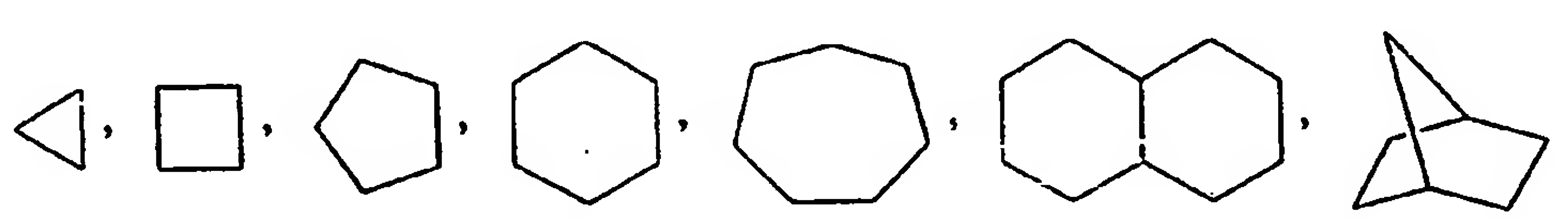
with the proviso that when R_{57} is H, R_{58} is a moiety other than H;

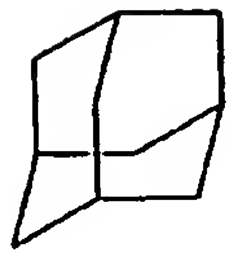
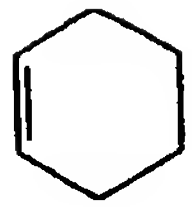
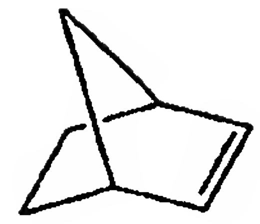
and pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof.

As used in the present application, the following definitions apply:

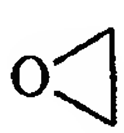
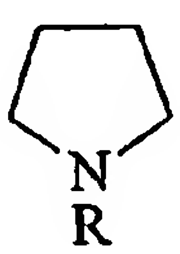
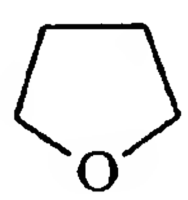
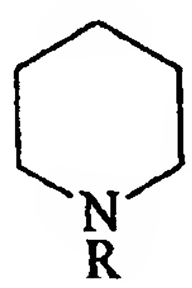
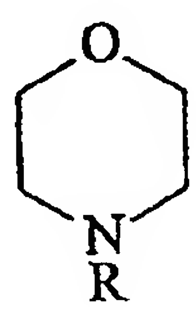
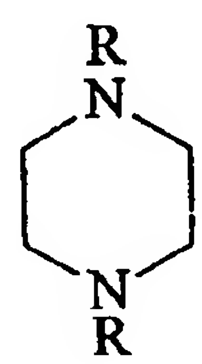
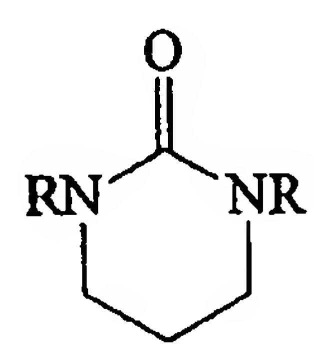
An "alkyl group" is intended to mean a straight or branched chain monovalent radical of saturated and/or unsaturated carbon atoms and hydrogen atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, pentenyl, butenyl, propenyl, ethynyl, butynyl, propynyl, pentynl, hexynyl, and the like, which may be unsubstituted (i.e., containing only carbon and hydrogen) or substituted by one or more suitable substituents as defined below.

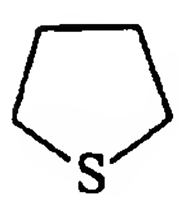
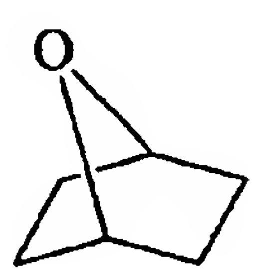
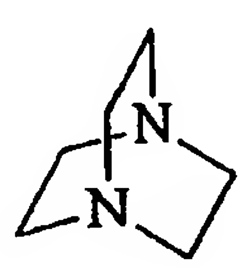
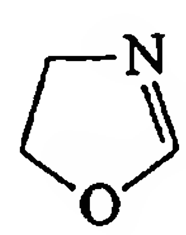
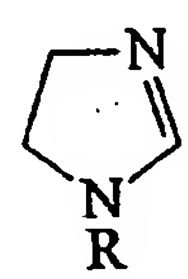
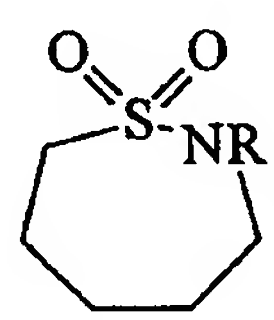
A "cycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon ring atoms, each of which may be saturated or unsaturated, and which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more heterocycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:

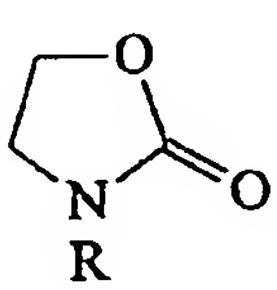
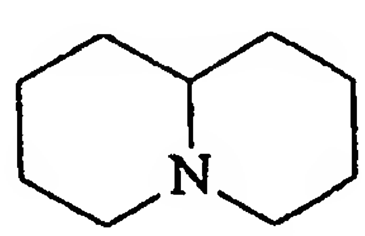
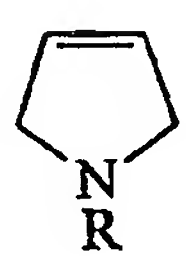
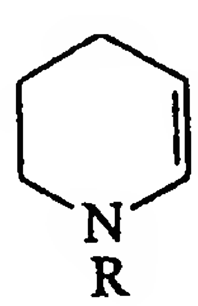
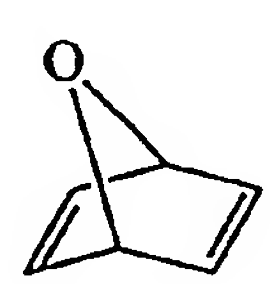


, , and .

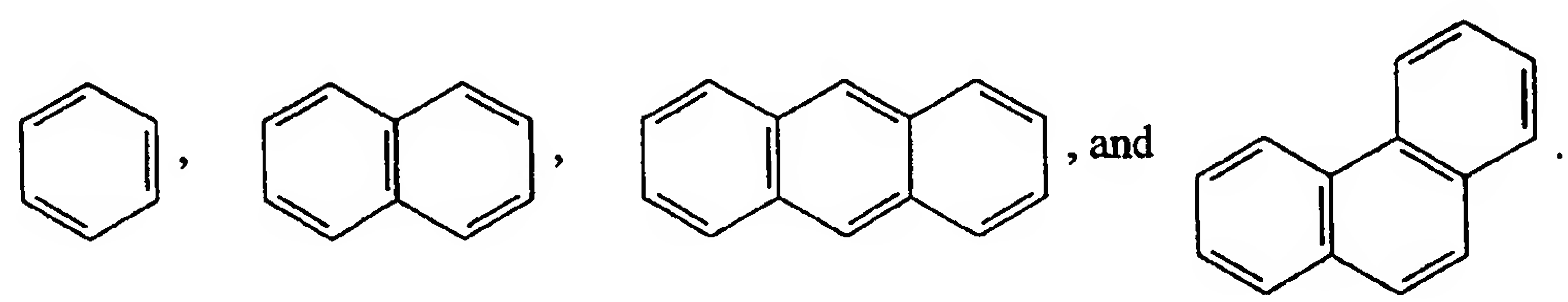
A "heterocycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or unsaturated, containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, and which includes 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein the radical is unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heterocycloalkyl groups include, but are not limited to the following moieties:

, , , , , , ,

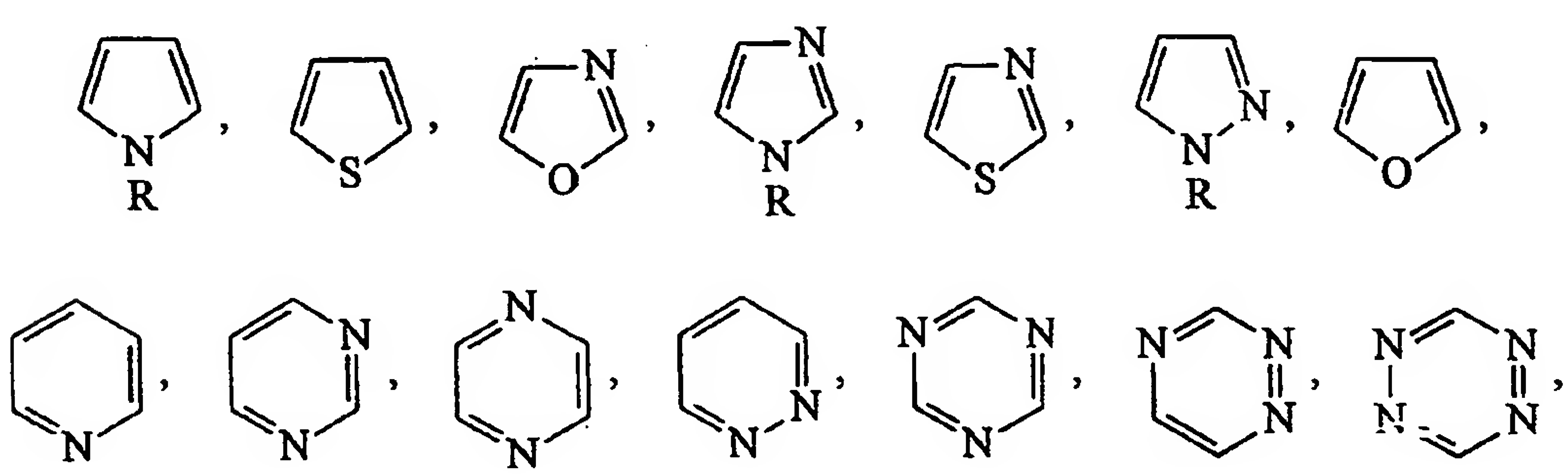
, , , , , ,

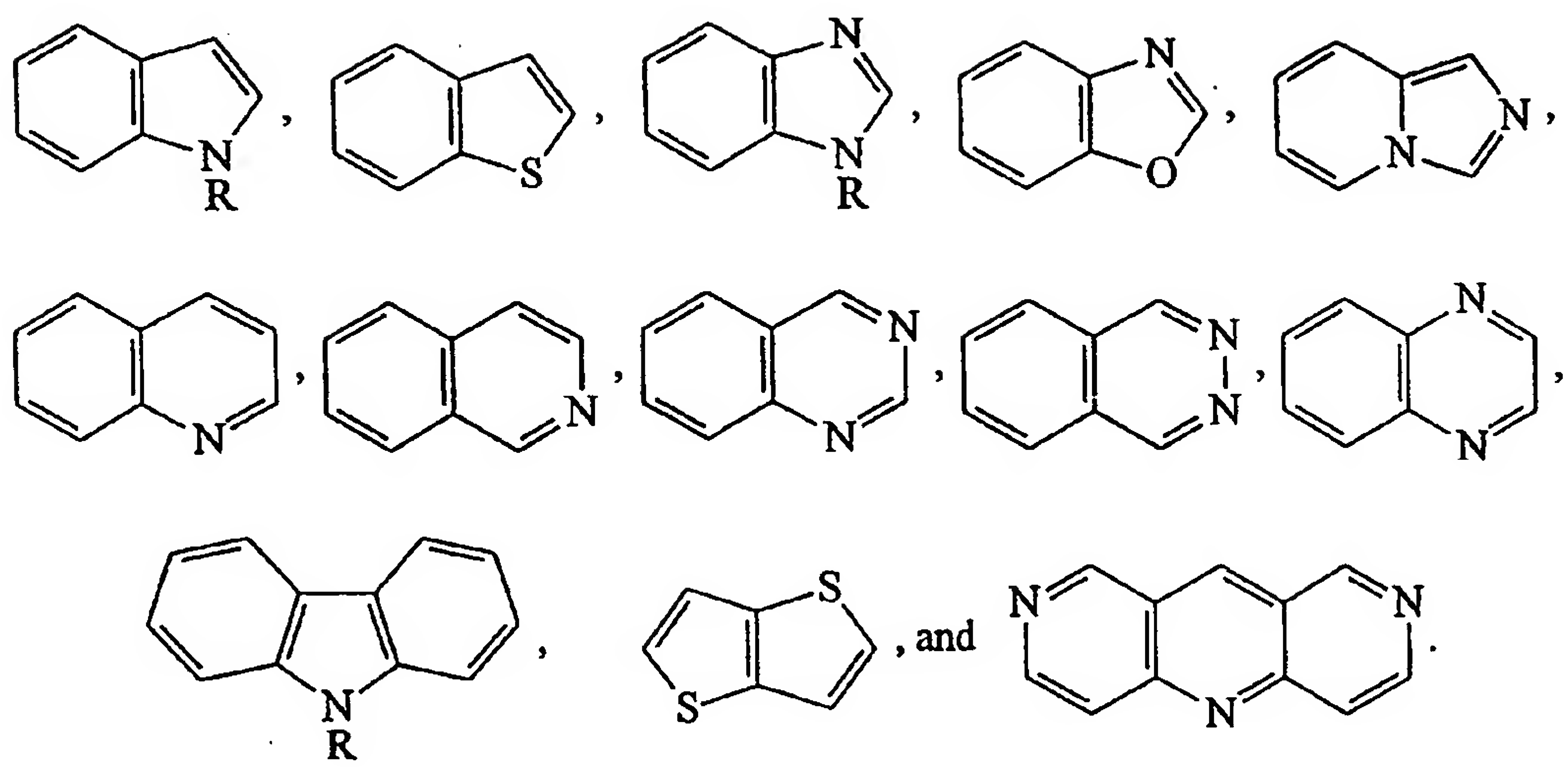
, , , , and .

An "aryl group" is intended to mean an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 6, 10, 14, or 18 carbon ring atoms, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of aryl groups include, but are not limited to, the following moieties:



A "heteroaryl group" is intended to mean an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, including 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or aryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heteroaryl groups include, but are not limited to, the following moieties:





An "acyl group" is intended to mean a −C(O)−R radical, wherein R is any suitable substituent as defined below.

A "thioacyl group" is intended to mean a −C(S)−R radical, wherein R is any suitable substituent as defined below.

A "sulfonyl group" is intended to mean a $-SO_2R$ radical, wherein R is any suitable substituent as defined below.

The term "suitable substituent" is intended to mean any of the substituents recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable substituents include, but are not limited to, hydroxy groups, oxo groups, alkyl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups,

aryloxy groups, heteroarlyoxy groups, arylthio groups, heteroarylthio groups, and the like.

The term "suitable organic moiety" is intended to mean any organic moiety recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable organic moieties include, but are not limited to, hydroxy groups, alkyl groups, oxo groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, arylthio groups, heteroarylthio groups, and the like.

A "hydroxy group" is intended to mean the radical -OH.

An "amino group" is intended to mean the radical $-NH_2$.

An "alkylamino group" is intended to mean the radical -NHR where R is an alkyl group as defined above.

A "dialkylamino group" is intended to mean the radical $-NR_aR_b$ where R_a and R_b are each independently an alkyl group as defined above.

An "alkoxy group" is intended to mean the radical -OR where R is an alkyl group as defined above, for example, methoxy, ethoxy, propoxy, and the like.

An "alkoxycarbonyl group" is intended to mean the radical –C(O)OR where R is an alkyl group as defined above.

An "alkylsulfonyl group" is intended to mean the radical $-SO_2R$ where R is an alkyl group as defined above.

An "alkylaminocarbonyl group" is intended to mean the radical $-C(O)NHR$ where R is an alkyl group as defined above.

A "dialkylaminocarbonyl group" is intended to mean the radical $-C(O)NR_aR_b$ where R_a and R_b are each independently an alkyl group as defined above.

A "mercapto group" is intended to mean the radical -SH.

An "alkylthio group" is intended to mean the radical -SR where R is an alkyl group as defined above.

A "carboxy group" is intended to mean the radical -C(O)OH.

A "carbamoyl group" is intended to mean the radical $-C(O)NH_2$.

An "aryloxy group" is intended to mean the radical $-OR_c$ where R_c is an aryl group as defined above.

A "heteroarlyoxy group" is intended to mean the radical $-OR_d$ where R_d is a heteroaryl group as defined above.

An "arylthio group" is intended to mean the radical $-SR_c$ where R_c is an aryl group as defined above.

A "heteroarylthio group" is intended to mean the radical $-SR_d$ where R_d is a heteroaryl group as defined above.

A "pharmaceutically acceptable prodrug" is intended to mean a compound that may be converted under physiological conditions or by solvolysis to a compound of formula I.

A "pharmaceutically acceptable active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a compound of formula I.

A "pharmaceutically acceptable solvate" is intended to mean a solvate that retains the biological effectiveness and properties of the biologically active components of compounds of formula I.

Examples of pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

A "pharmaceutically acceptable salt" is intended to a mean a salt that retains the biological effectiveness and properties of the free acids and bases of compounds of formula I and that is not biologically or otherwise undesirable.

Examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric

acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acids such as glucuronic acid and galacturonic acid, alpha-hydroxy acids such as citric acid and tartaric acid, amino acids such as aspartic acid and glutamic acid, aromatic acids such as benzoic acid and cinnamic acid, sulfonic acids such a p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary and tertiary amines, and cyclic amines such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention.

The inventive compounds may exist as single stereoisomers, racemates and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive compounds are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound which comprises at least a sufficient amount of a single enantiomer to yield a compound having the desired pharmacological activity. Preferably, "optically pure" is intended to mean a compound that comprises at least 90% of a single isomer (80% enantiomeric excess), preferably at least 95% (90% e.e.), more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

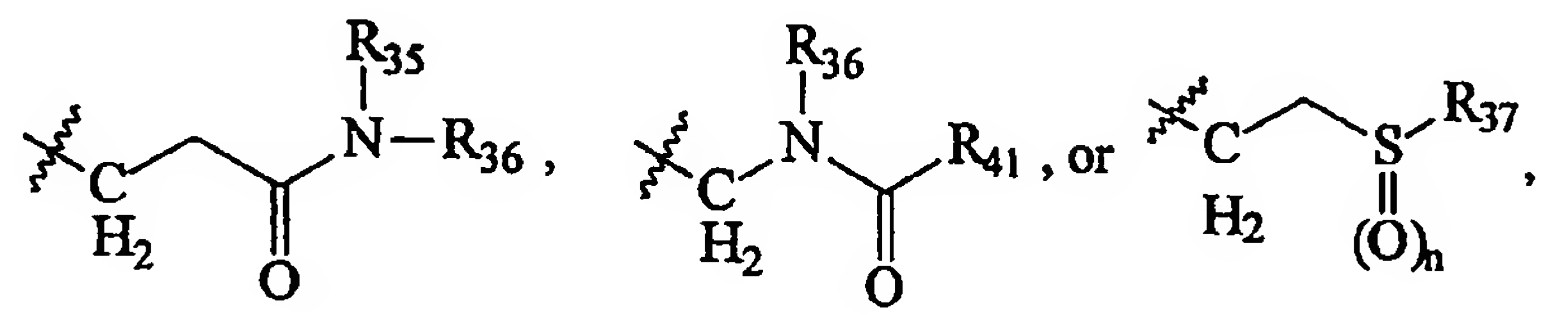
Preferably in the above formulas I and II, R_1 and R_{51} are H or F. Preferably in the compounds of formula I, at least one of R_4 and R_8 is an acyl group or a sulfonyl group. Preferably in the above formulas I and II, D_1 and D_2 are $-OR_{25}$, $=O$, $=S$, $\equiv N$, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group, and more preferably D_1 and D_2 are $=O$. Preferably A_1 and A_2 are C, CH, S, or S(O), and more preferably A_1 and A_2 are C.

Preferably B_1 and B_2 are $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein R_{17} and R_{18}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group.

Preferably Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$; wherein R_{21}, R_{22}, and R_{23} are independently

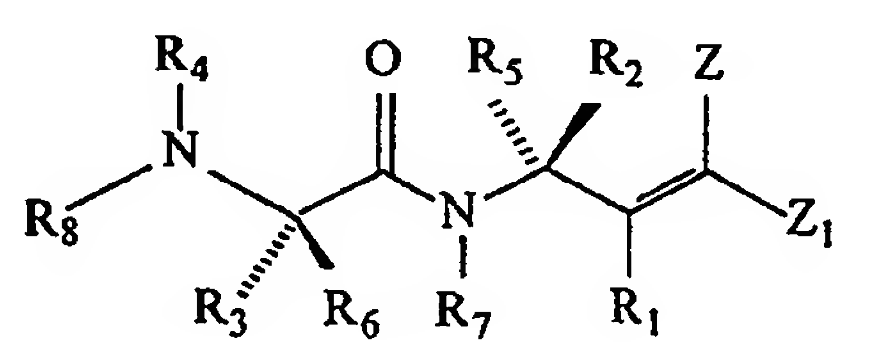
H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein any two of R_{21}, R_{22}, and R_{23}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, or Z and Z_1, together with the atoms to which they are attached, form a heterocycloalkyl group. Preferably M is O.

Preferably R_{52} is one of the following moieties:



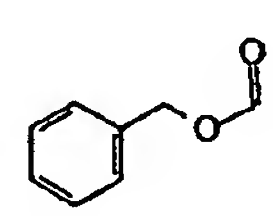
wherein R_{35}, R_{36}, R_{37}, R_{41}, and n are as defined above.

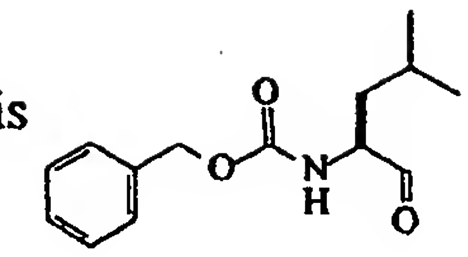
Compounds according to formula I include those described below, where * indicates the point of attachment. For example, the invention includes compounds 1–17 having the formula Ia:



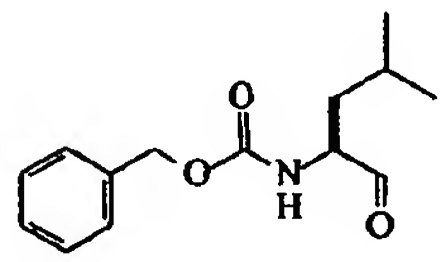
(Ia),

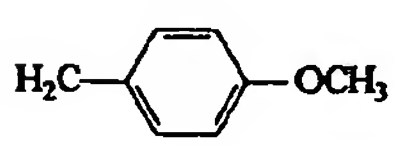
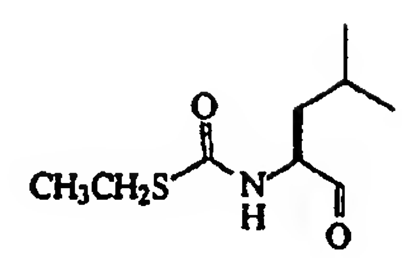
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

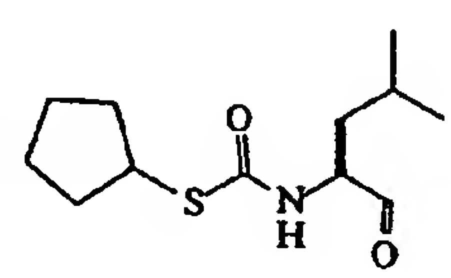
1. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

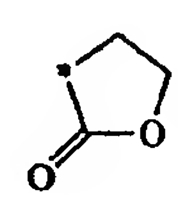
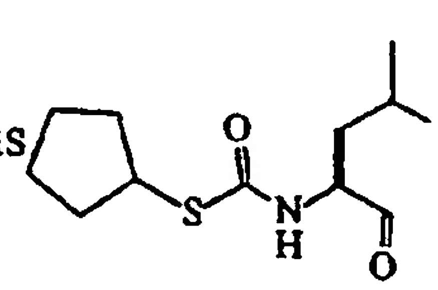
2. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

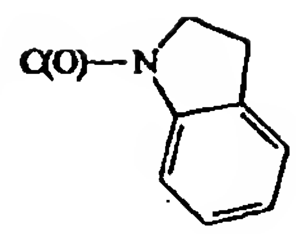
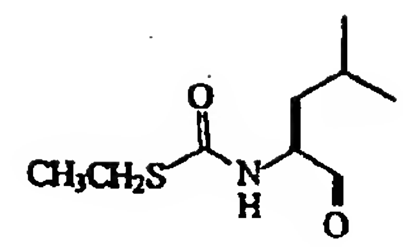
3. Z is H, Z_1 is $CO_2CH_2CH_3$, R_3 is  and

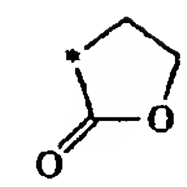
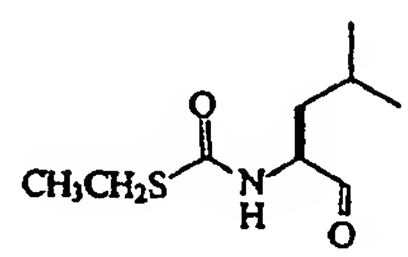
R_8 is  ;

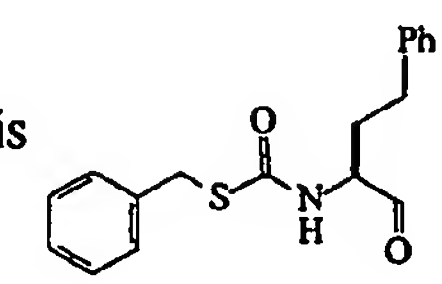
4. R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

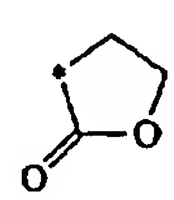
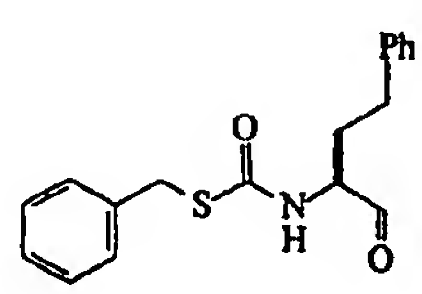
5. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

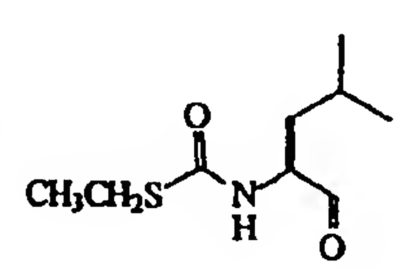
6. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group is preferably cis to the R_1 group), and R_8 is  ;

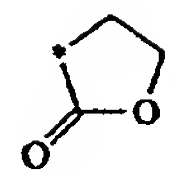
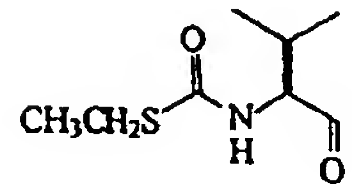
7. R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is ;

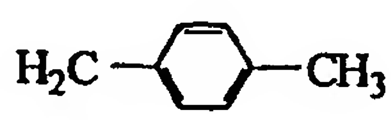
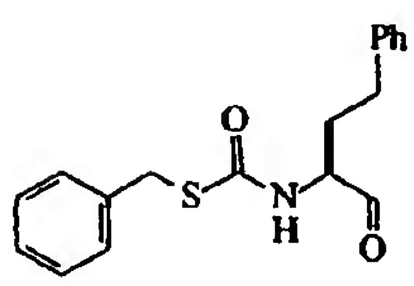
8. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group is preferably cis to the R_1 group), and R_8 is ;

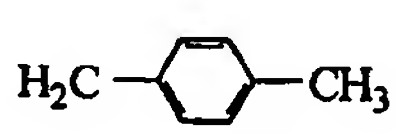
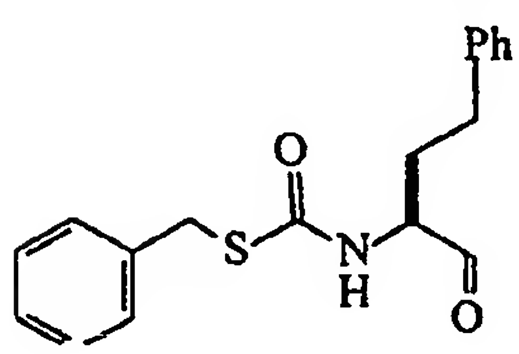
9. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

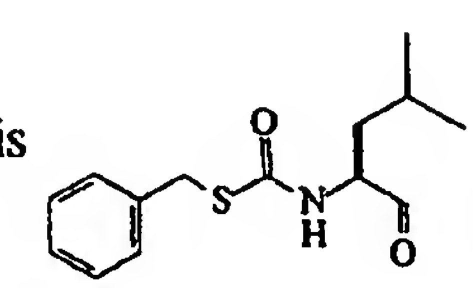
10. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group preferably is cis to the R_1 group), and R_8 is ;

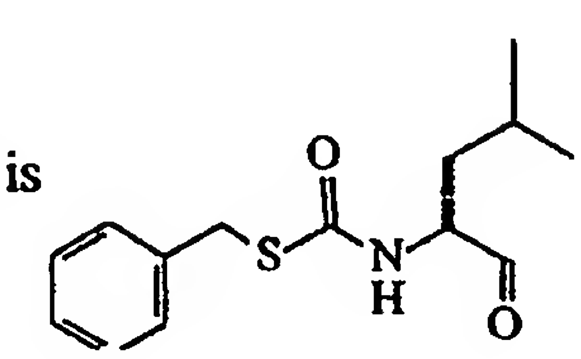
11. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

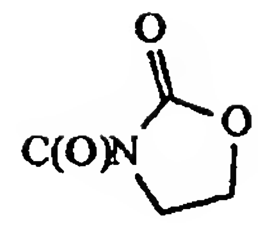
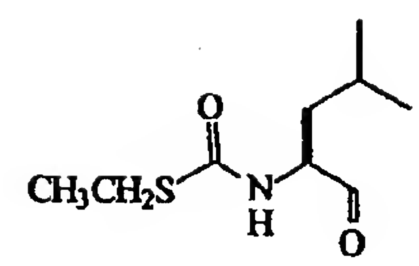
12. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group preferably is cis to the R_1 group), and R_8 is ;

13. R_3 is , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

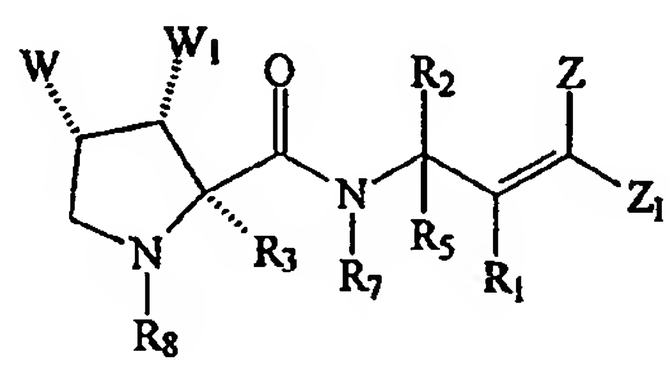
14. R_3 is , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

15. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

16. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is ; and

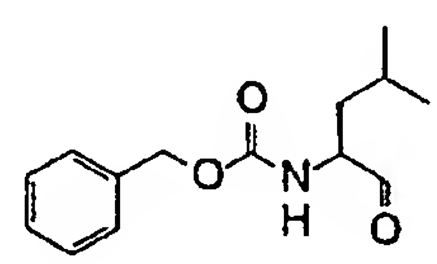
17. R_3 is CH_2Ph, Z is H, Z_1 is  and R_8 is  .

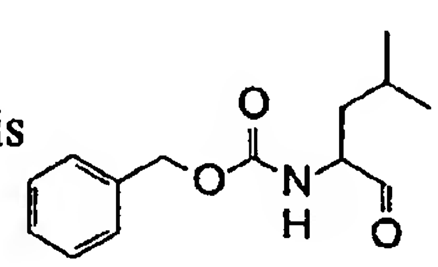
Additional compounds according to the invention include compounds **18-24** having the formula Ib:

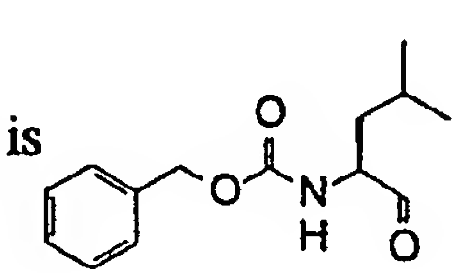


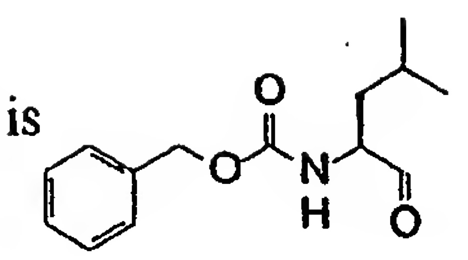
(Ib),

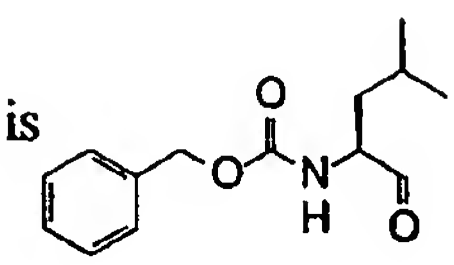
wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, and Z_1, W, W_1, and R_8 are selected from one of the following groups:

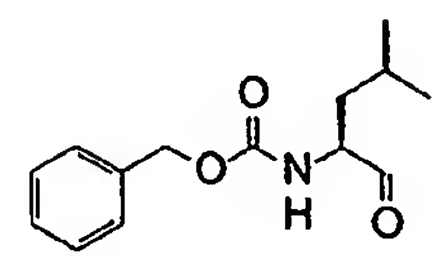
18. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is Ph, and R_8 is  ;

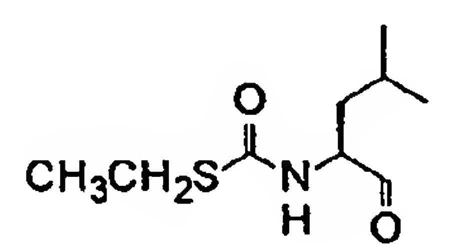
19. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  ;

20. Z_1 is $CO_2CH_2CH_3$, W is OCH_2Ph, W_1 is H, and R_8 is  ;

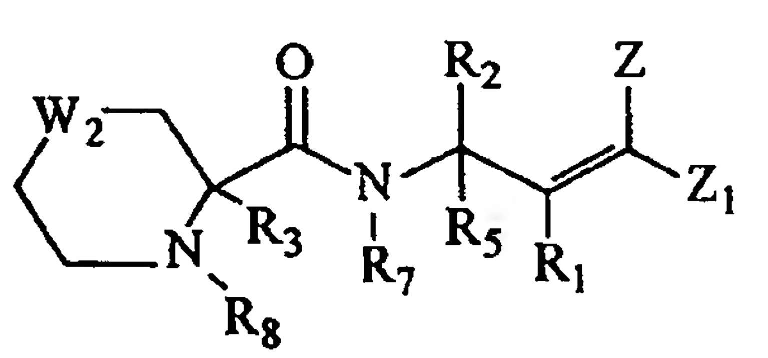
21. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is CH_3, and R_8 is  ;

22. Z_1 is $C(O)N(CH_3)OCH_3$, W is H, W_1 is Ph, and R_8 is  ;

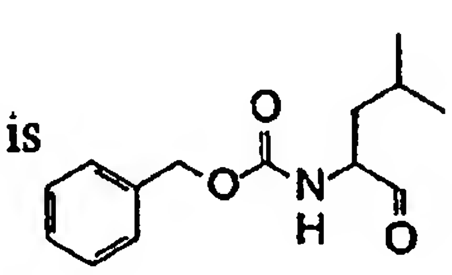
23. Z_1 is $CO_2CH_2CH_3$, W is $OC(CH_3)_3$, W_1 is H, and R_8 is  ; and

24. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  .

The invention further includes compounds **25-29** having the formula Ic:

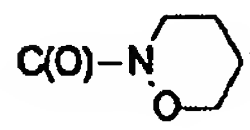


(Ic),

wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_8 is  ,

and W_2 and Z_1 are selected from one of the following groups:

25. W_2 is CH_2 and Z_1 is $CO_2CH_2CH_3$;

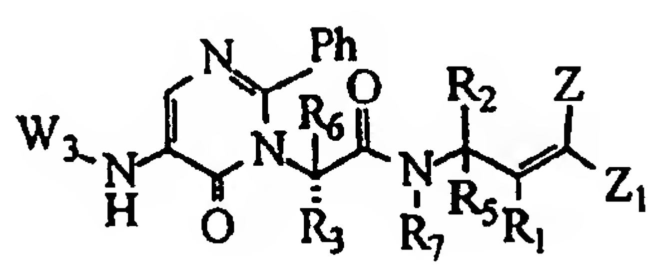
26. W_2 is CH_2 and Z_1 is ;

27. W_2 is NH and Z_1 is $CO_2CH_2CH_3$;

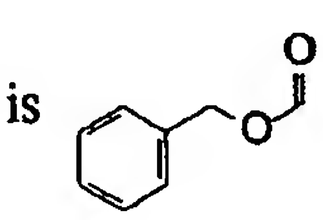
28. W_2 is NCH_2Ph and Z_1 is $CO_2CH_2CH_3$; and

29. W_2 is NSO_2Ph and Z_1 is $CO_2CH_2CH_3$.

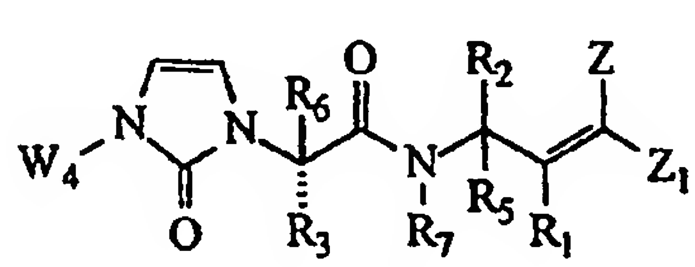
Additionally, the invention includes compounds **30** and **31** according to formula Id:



(Id),

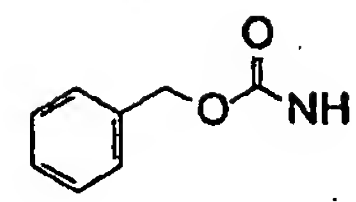
wherein R_1, R_3, R_5, R_6, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_3 is  in Compound 30, and W_3 is H in Compound 31.

The invention also includes compounds **32** and **33** according to formula Ie:

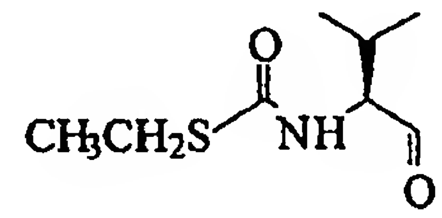


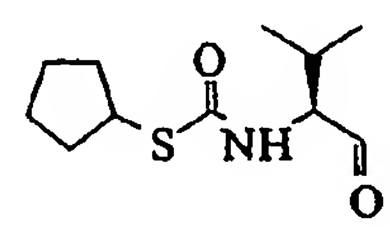
(Ie),

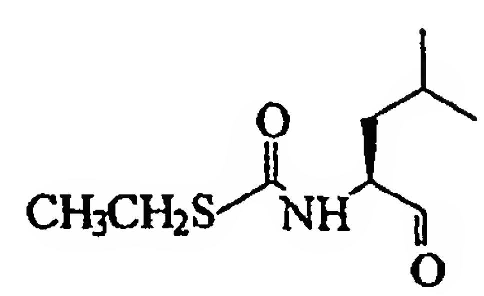
wherein R_1, R_5, R_6, R_7, and Z are each H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph,

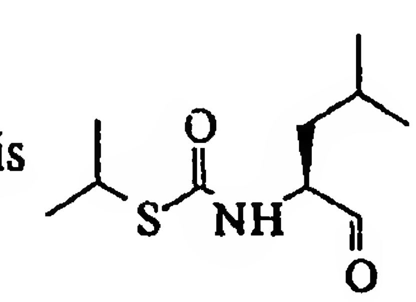
Z_1 is $CO_2CH_2CH_3$, and W_4 is H in Compound 32, and W_4 is  in Compound 33.

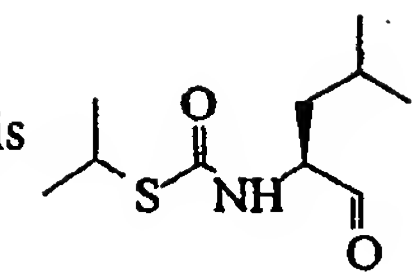
The invention further includes compounds **34-36**, **38-49**, and **56-58** also according to formula Ia above, wherein R_1, R_5, R_6, and R_7 are each H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

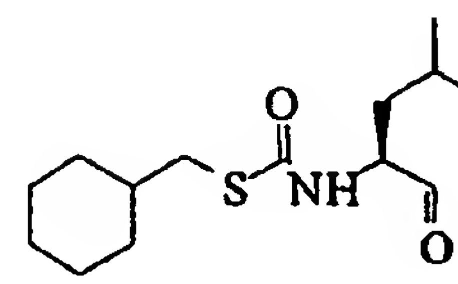
34. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

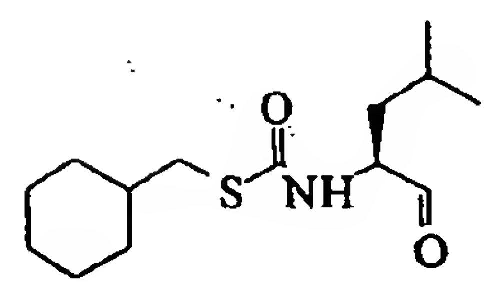
35. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

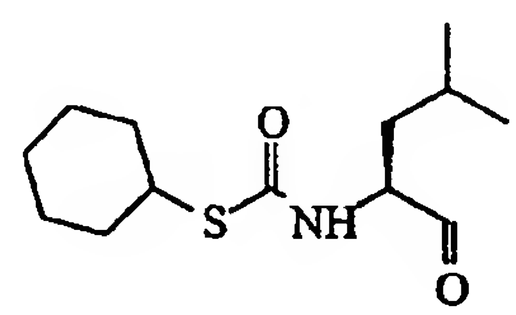
36. R_3 is CH_2Ph, Z is H, Z_1 is $C(O)N(CH_3)OCH_3$, and R_8 is  ;

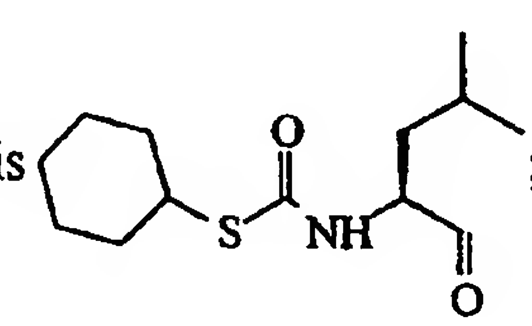
38. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

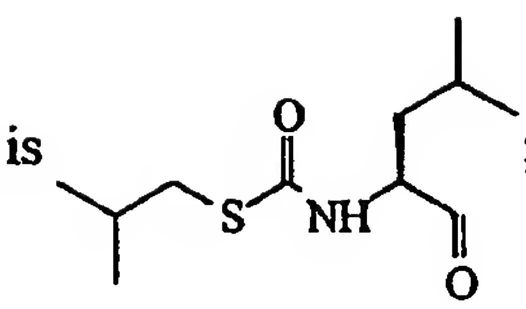
39. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

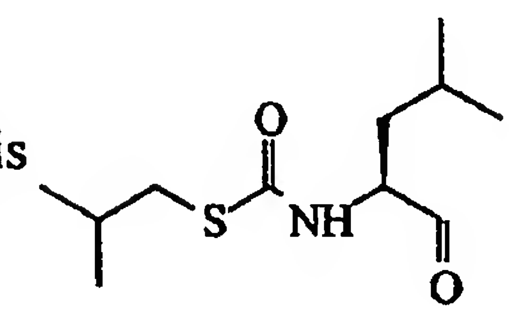
40. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

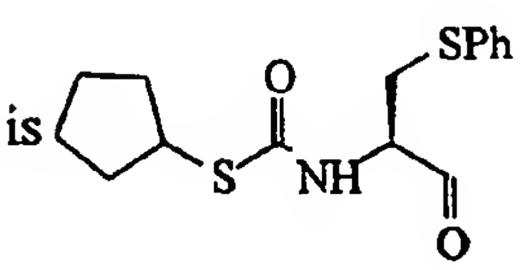
41. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

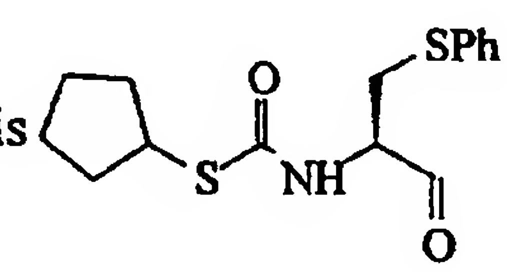
42. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

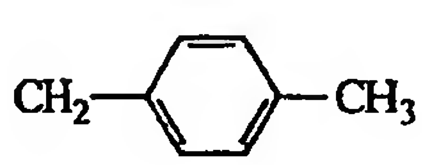
43. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

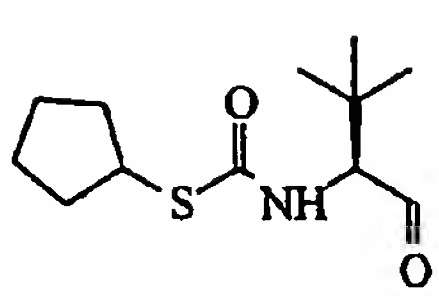
44. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

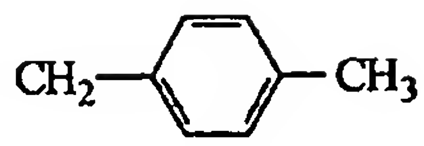
45. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

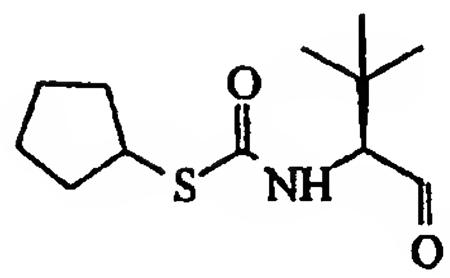
46. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

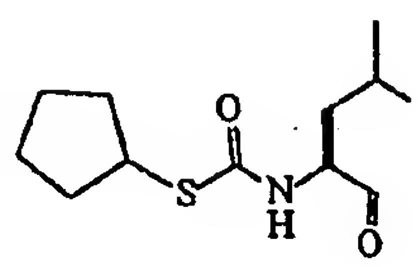
47. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

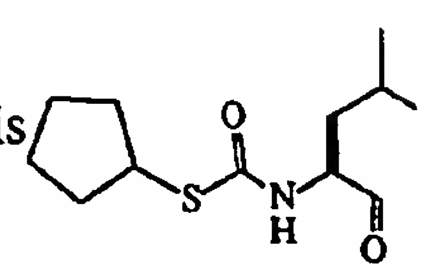
48. R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is

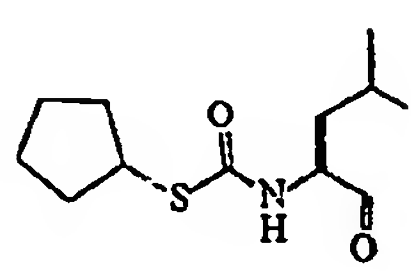
 ;

49. R_3 is , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is

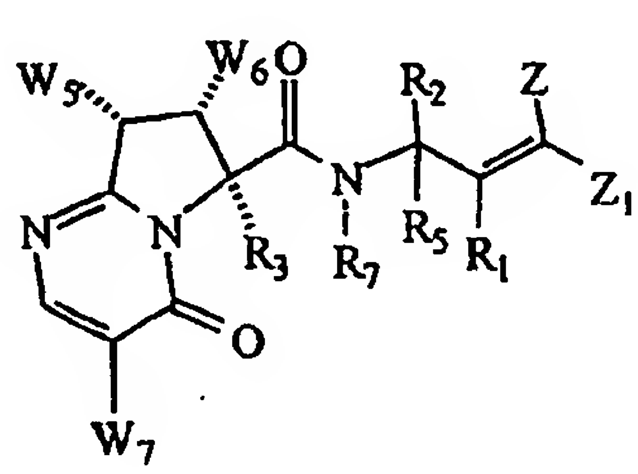
 ;

56. R_3 is CH_2Ph, Z is H, Z_1 is CO_2CH_2Ph, and R_8 is  ;

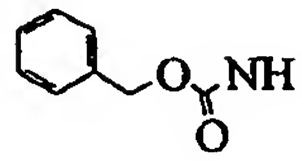
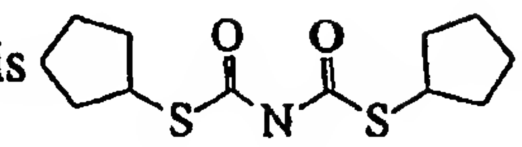
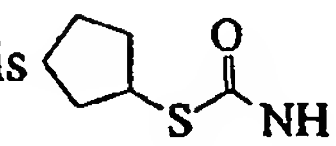
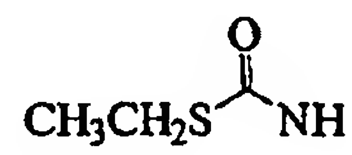
57. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2CH_3$, and R_8 is  ; and

58. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2OCH_3$, and R_8 is  .

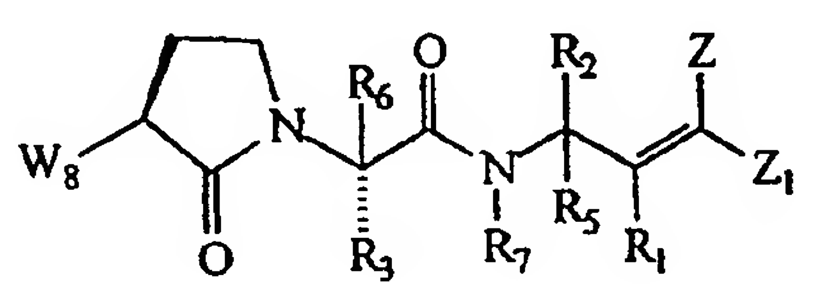
The invention also includes compounds **37** and **50–52** having the formula Ig:



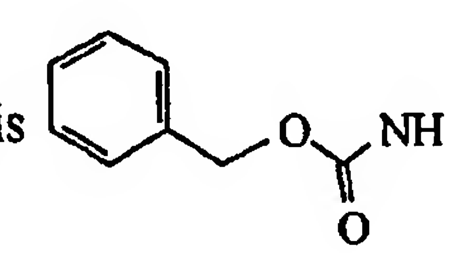
(Ig),

wherein R_1, R_3, R_5, R_7, W_5, W_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_7 is  in Compound 37, W_7 is  in Compound 50, W_7 is  in Compound 51, and W_7 is  in Compound 52.

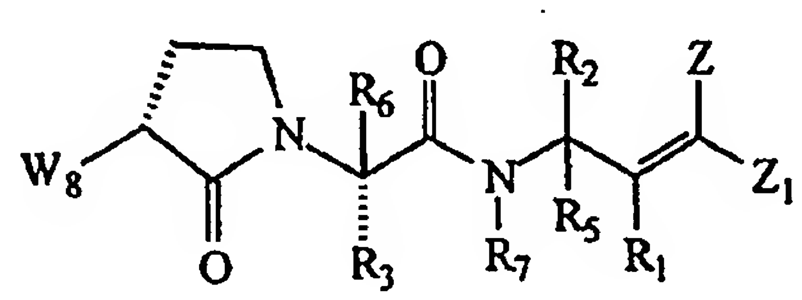
Compound **53** also corresponds to this invention. This compound has the formula Ih:



(Ih),

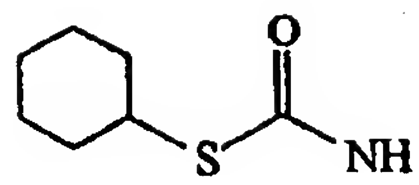
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and W_8 is .

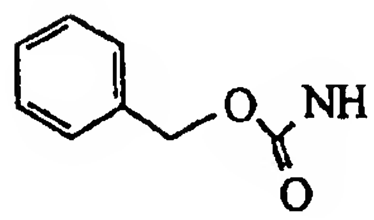
The invention also relates to compounds **54** and **55** having the formula (Ij):



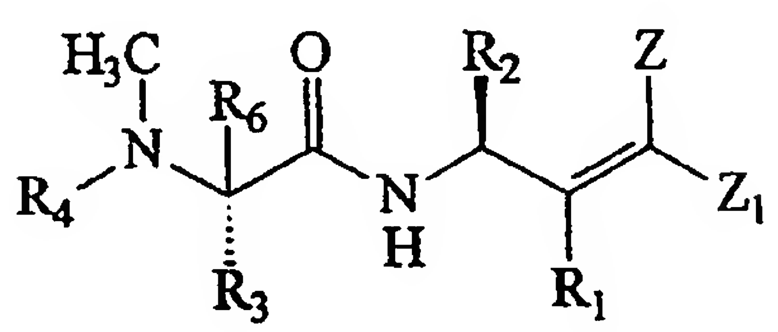
(Ij),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is

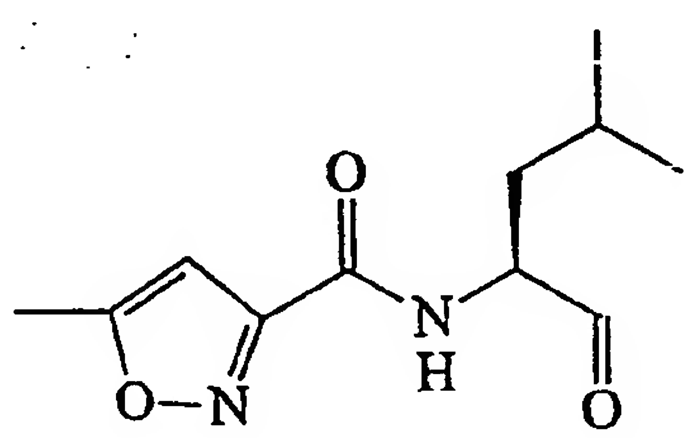
$CO_2CH_2CH_3$, and W_8 is  in Compound 54, and W_8 is

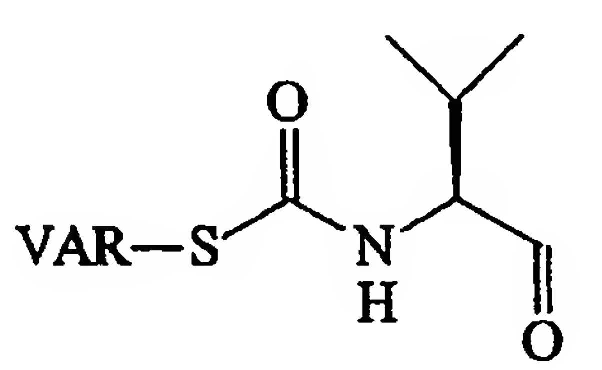
 in Compound 55.

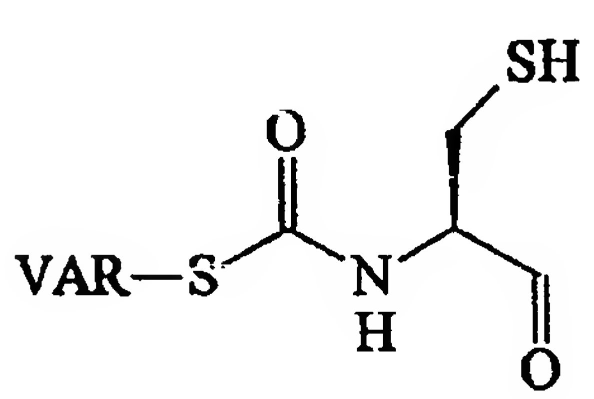
Other compounds according to the invention include the following compounds of formula X:

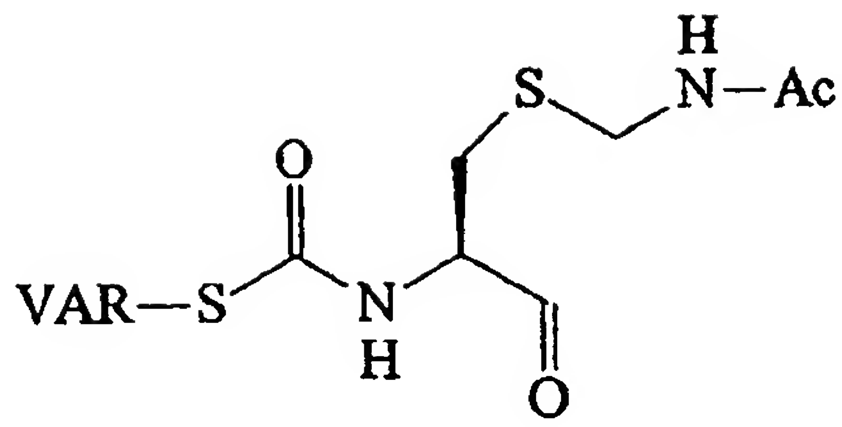
 (X),

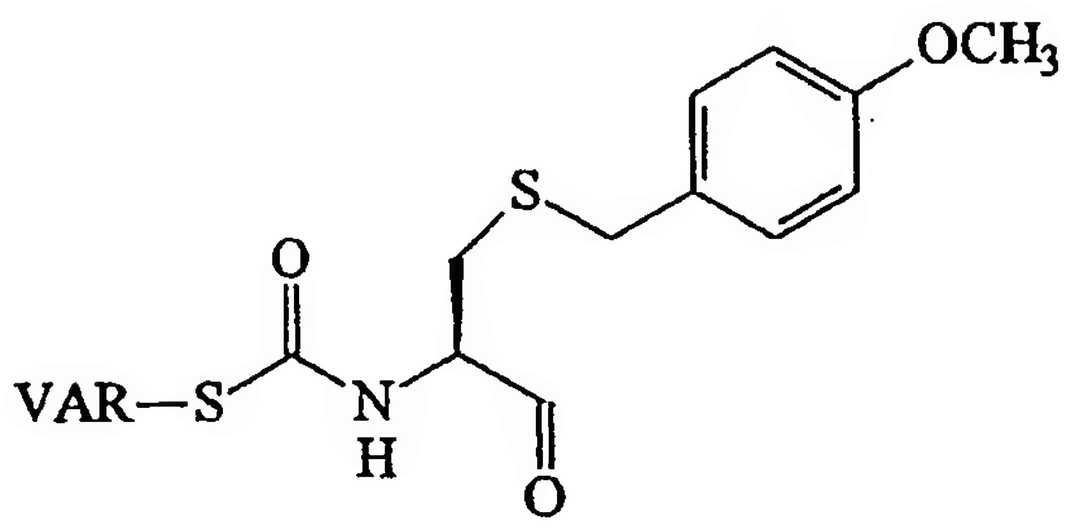
wherein R_1, R_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z_1 is $CO_2CH_2CH_3$, and R_4 is selected from one of the following:

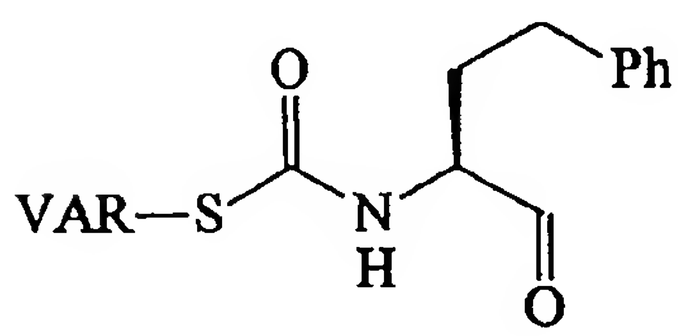
59. R_4 is  ;

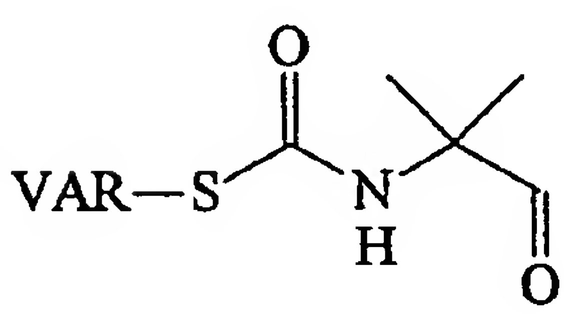
60. R_4 is  ;

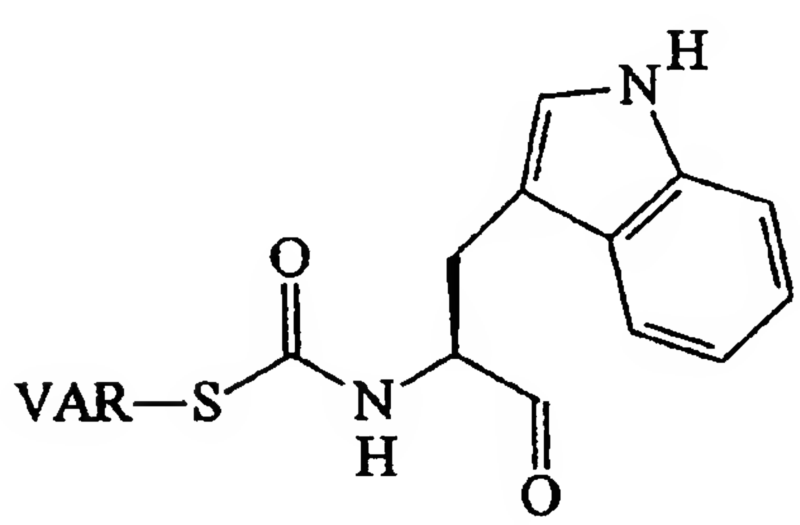
61. R_4 is  ;

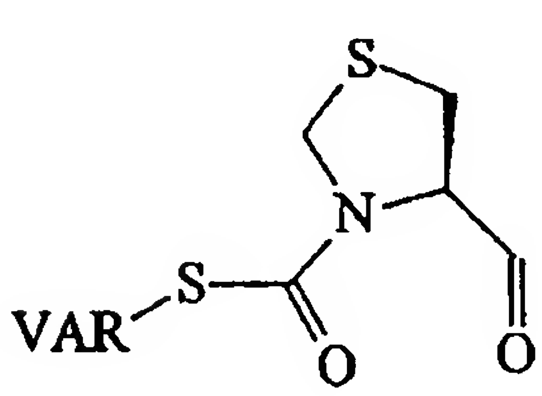
62. R_4 is  ;

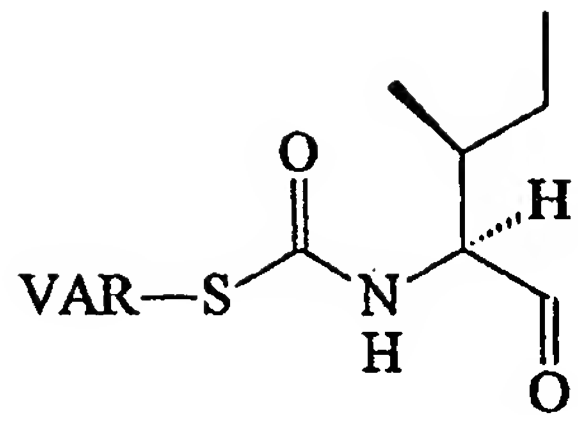
63. R_4 is  ;

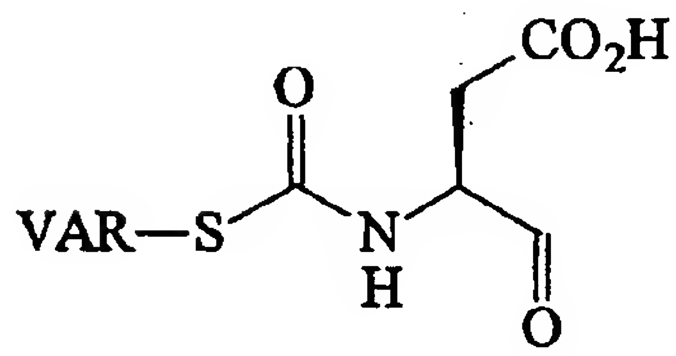
64. R_4 is  ;

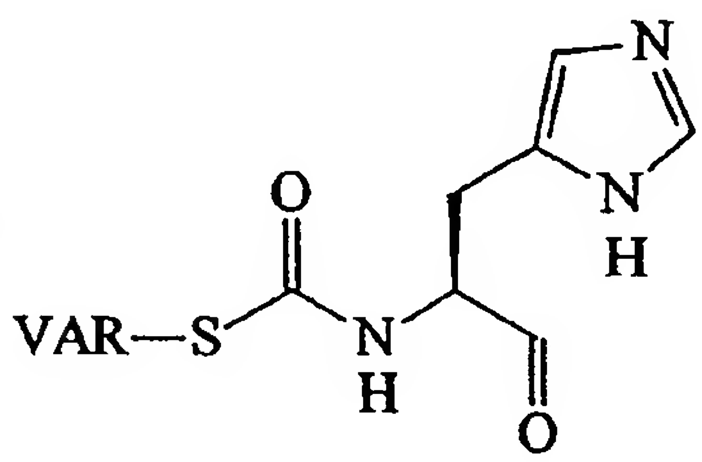
65. R_4 is  ;

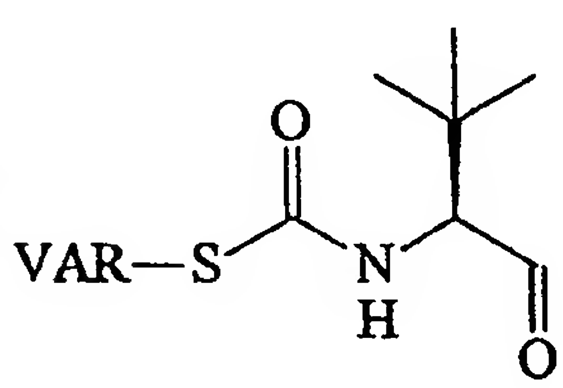
66. R_4 is  ;

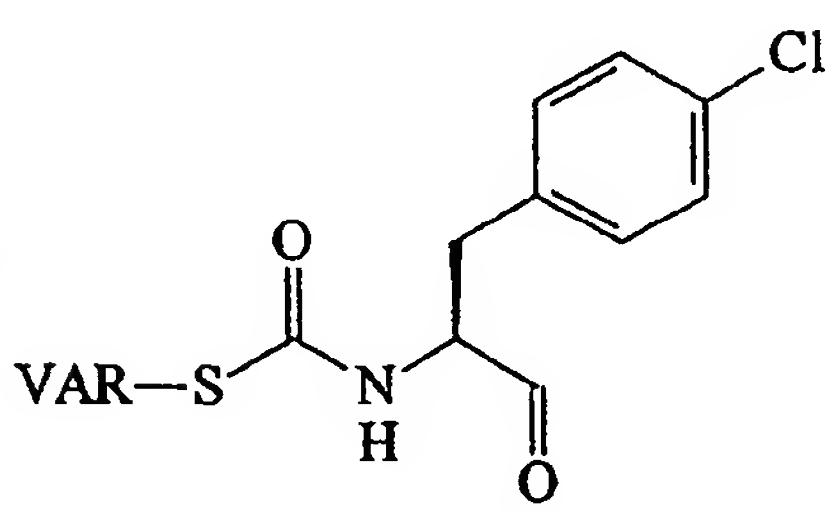
67. R_4 is  ;

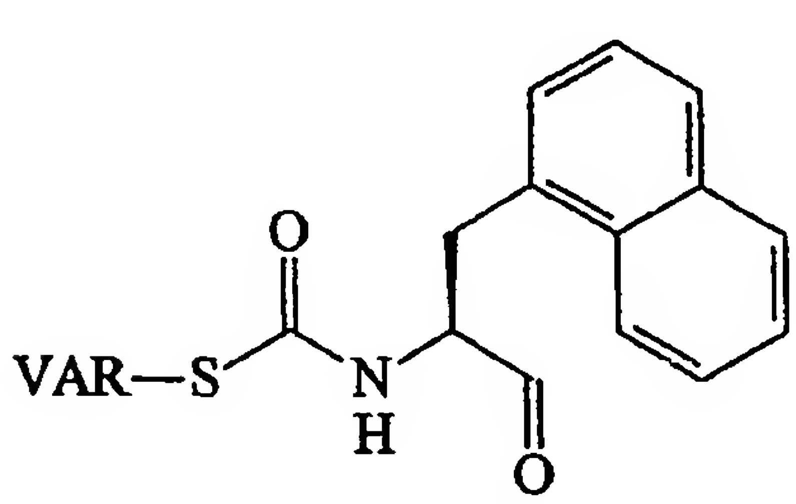
68. R_4 is  ;

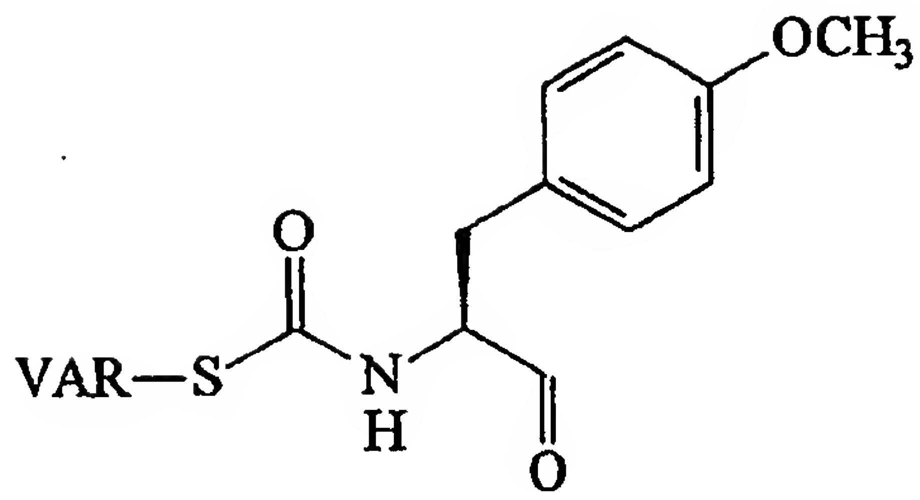
69. R_4 is  ;

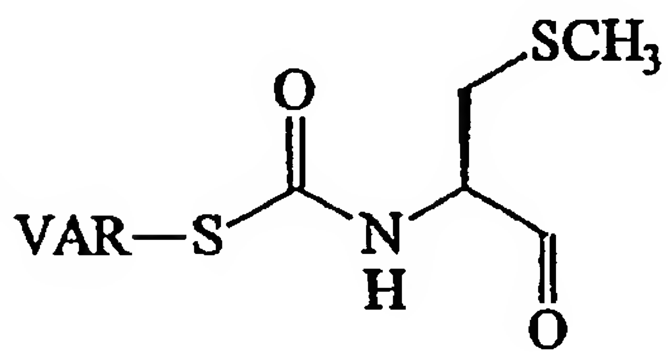
70. R_4 is  ;

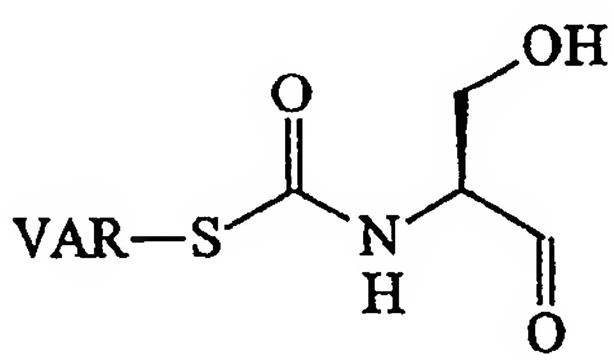
71. R_4 is  ;

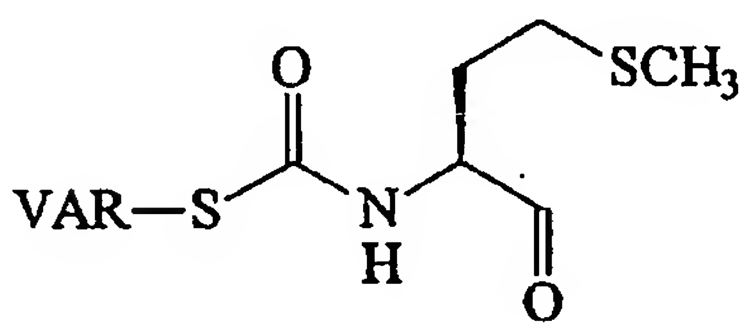
72. R_4 is  ;

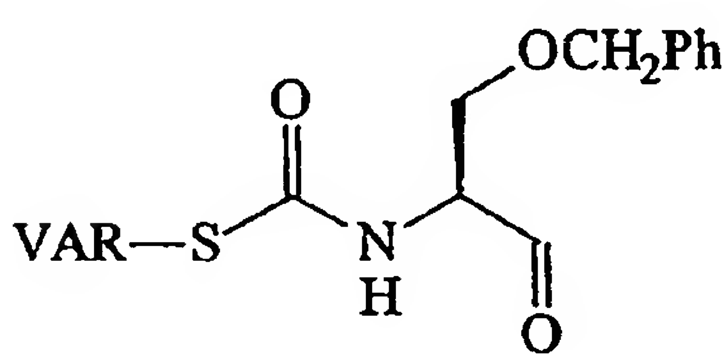
73. R_4 is  ;

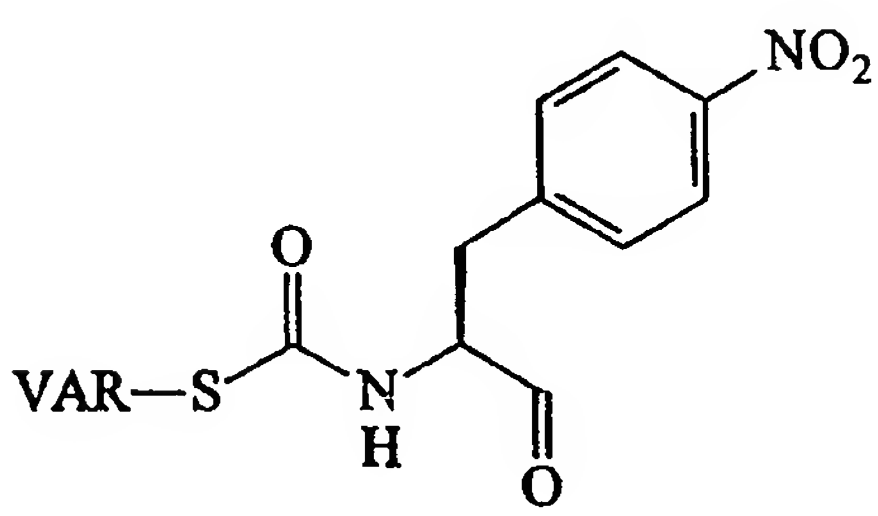
74. R_4 is  ;

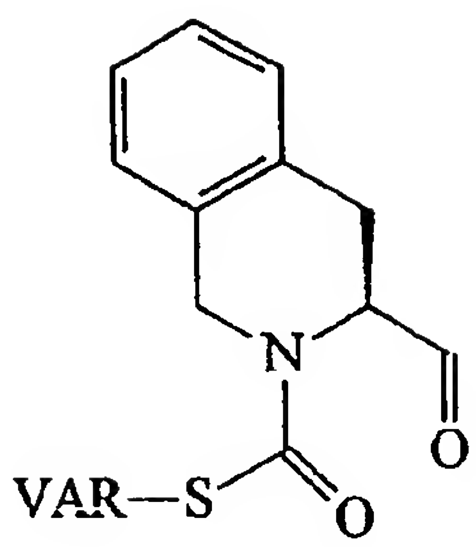
75. R_4 is  ;

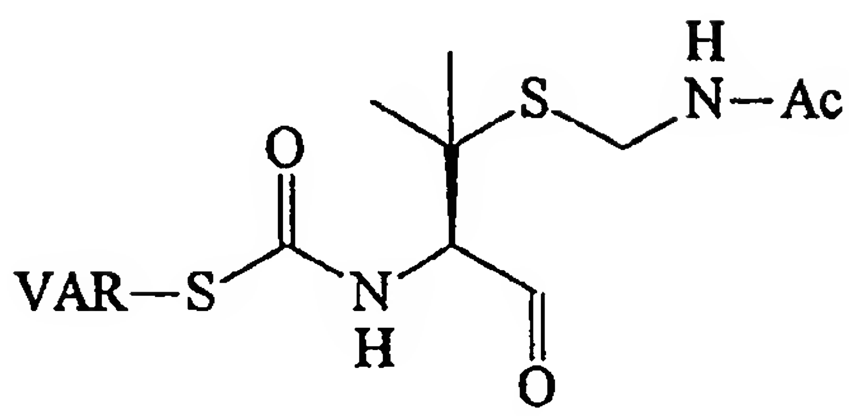
76. R_4 is  ;

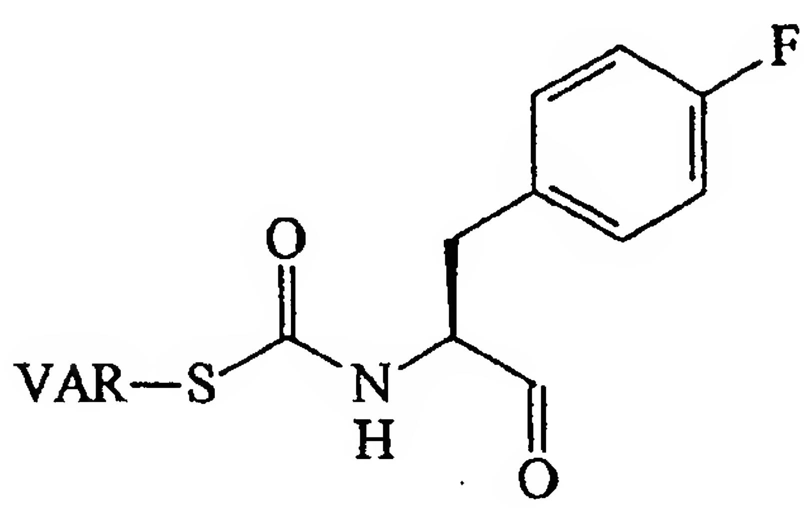
77. R_4 is  ;

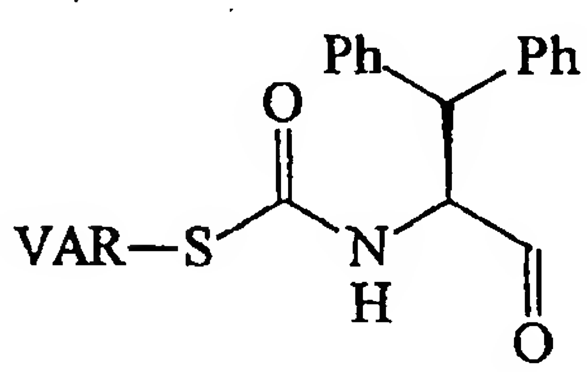
78. R_4 is  ;

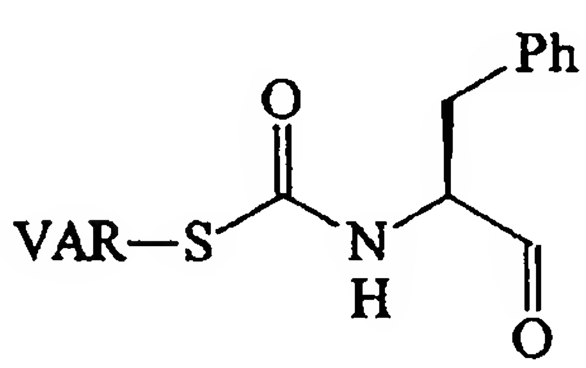
79. R_4 is  ;

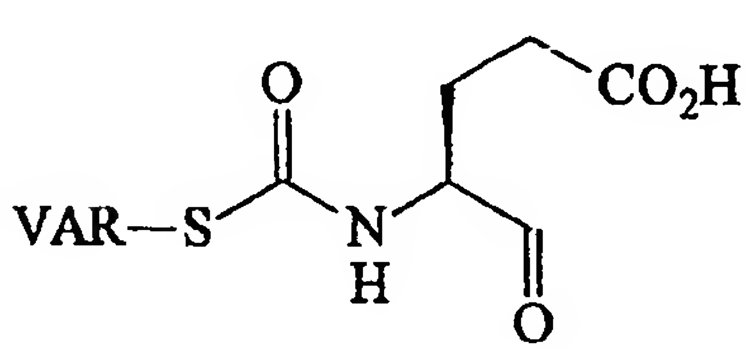
80. R_4 is  ;

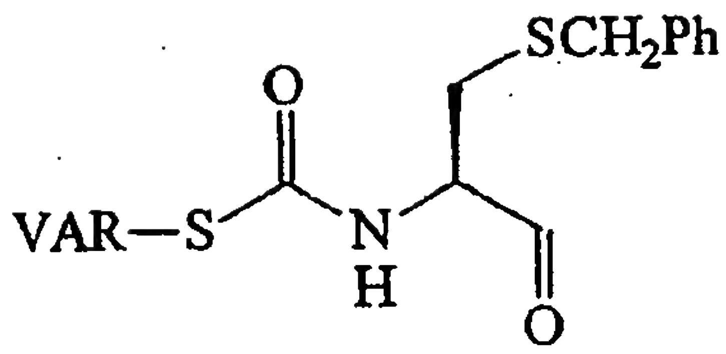
81. R_4 is  ;

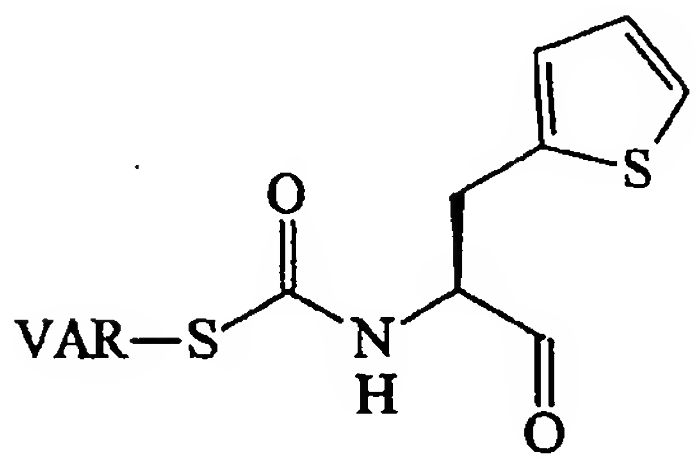
82. R_4 is  ;

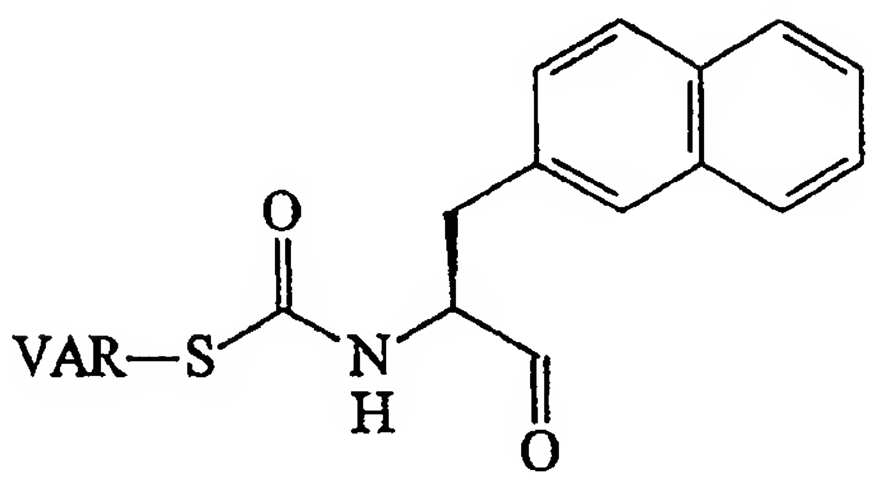
83. R_4 is  ;

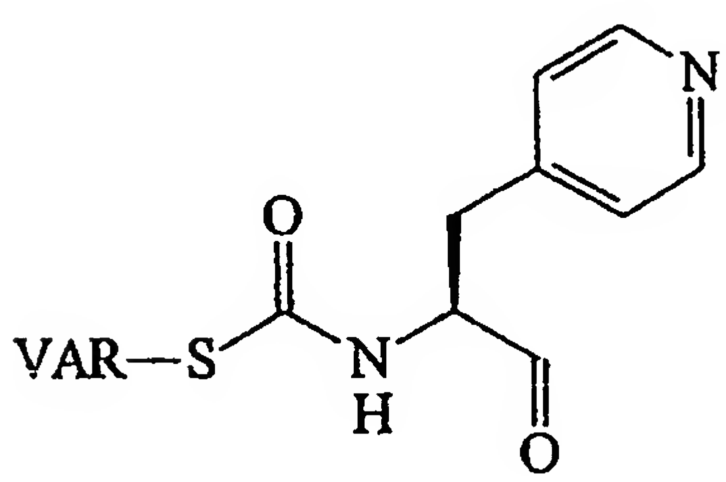
84. R_4 is  ;

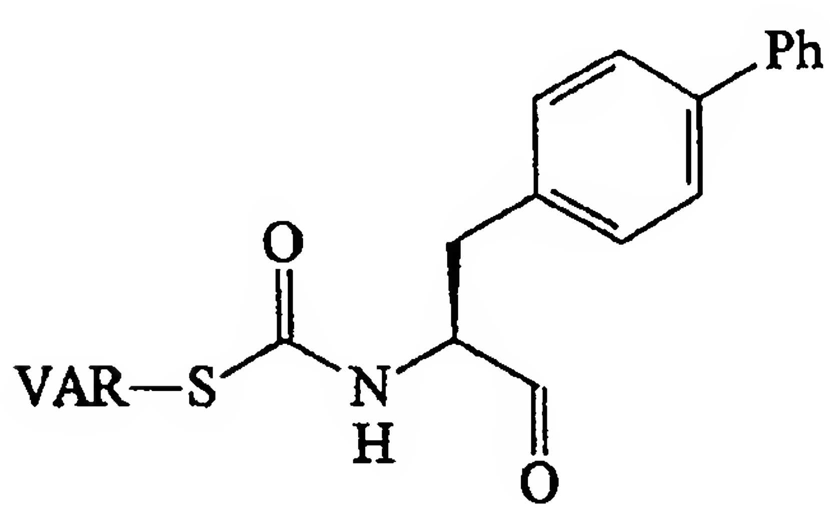
85. R_4 is  ;

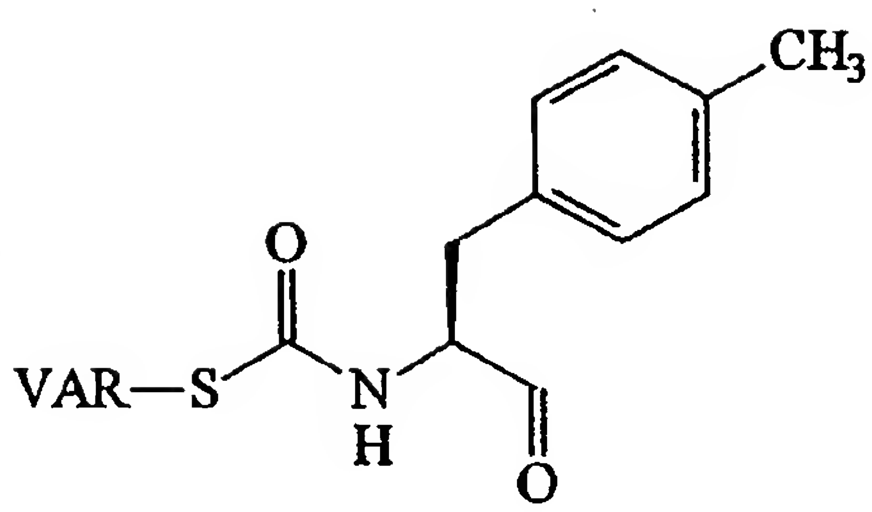
86. R_4 is  ;

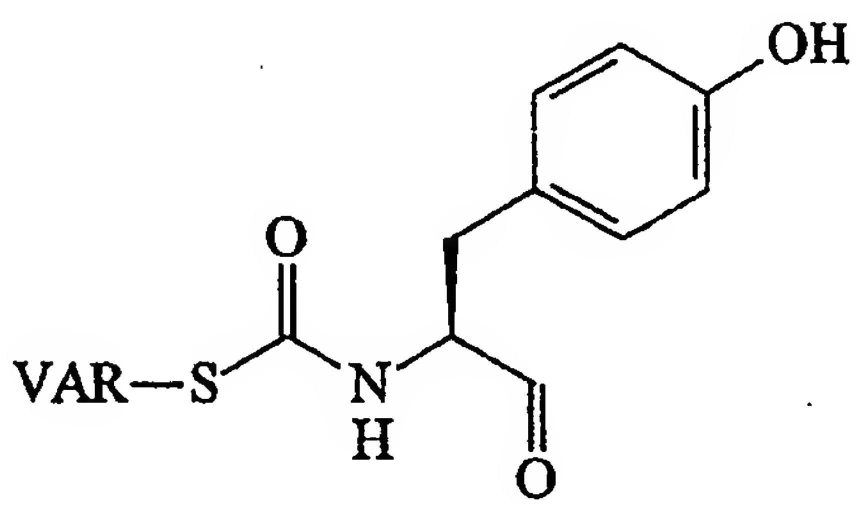
87. R_4 is  ;

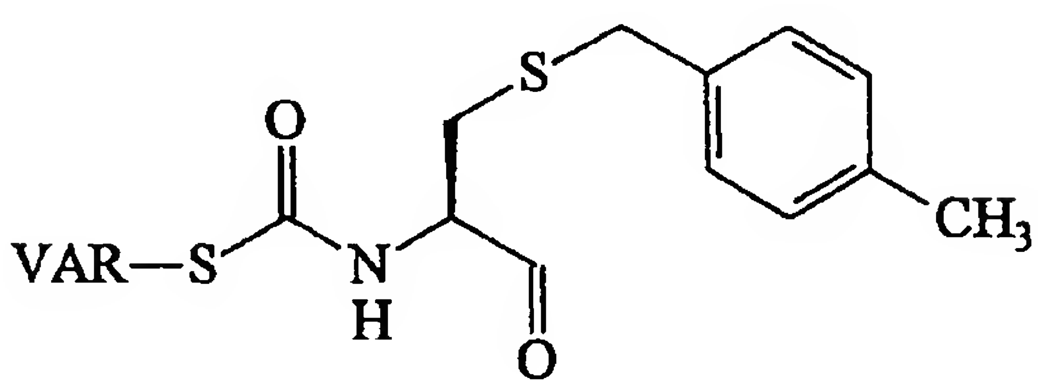
88. R_4 is  ;

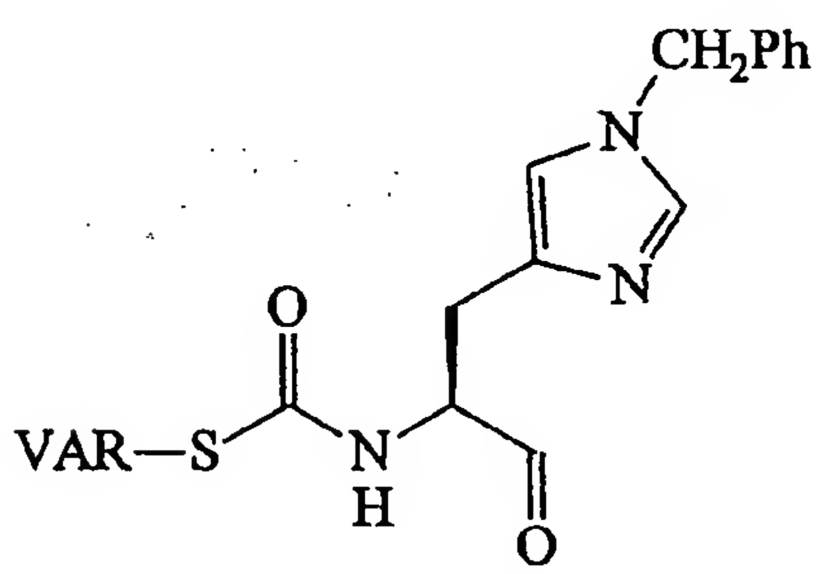
89. R_4 is  ;

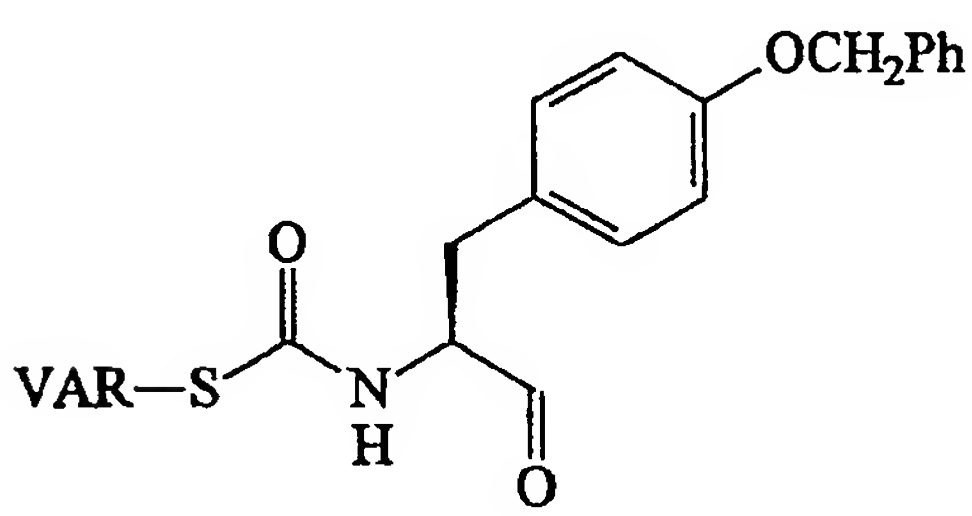
90. R_4 is  ;

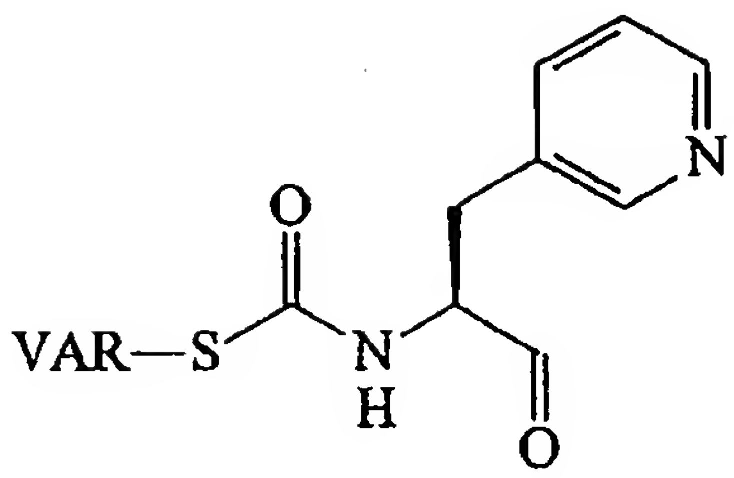
91. R_4 is  ;

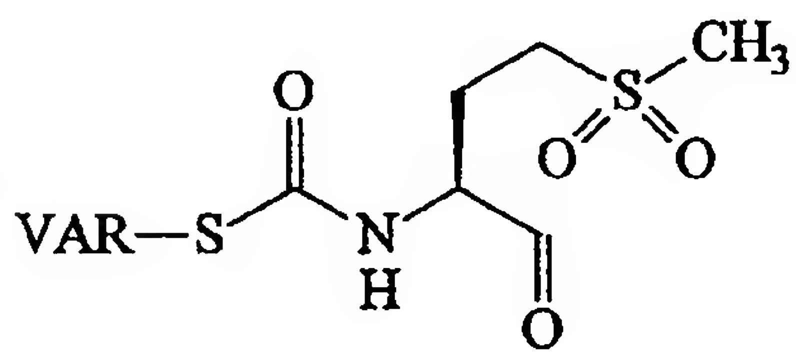
92. R_4 is  ;

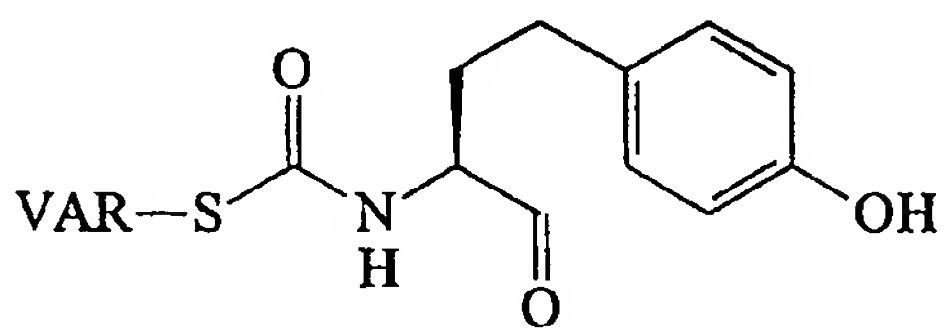
93. R_4 is  ;

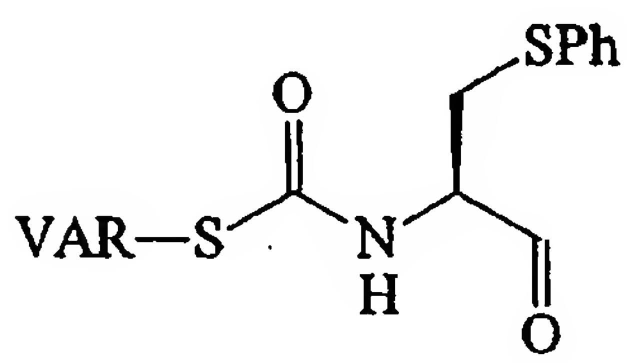
94. R_4 is  ;

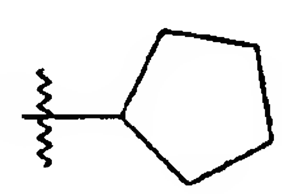
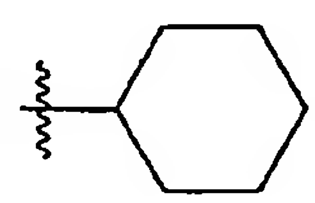
95. R_4 is  ;

96. R_4 is  ;

97. R_4 is  ;

98. R_4 is  ; and

99. R_4 is  ,

wherein VAR is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2Ph$, , and .

The present invention is further directed to methods of inhibiting picornaviral 3C protease activity that comprises contacting the protease for the purpose of such inhibition with an effective amount of a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof. For example, one can inhibit picornaviral 3C protease activity in mammalian tissue by administering a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate

thereof. More particularly, the present invention is directed to methods of inhibiting rhinoviral protease activity.

The activity of the inventive compounds as inhibitors of picornaviral 3C protease activity may be measured by any of the methods available to those skilled in the art, including in vivo and in vitro assays. Examples of suitable assays for activity measurements include the Antiviral HI-HeLa Cell Culture Assay and the Normal Human Bronchial Epithelial Cell Assay, both described herein.

Administration of the compounds of formula I, or their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates, may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include, but are not limited to, oral, nasal, parenteral, topical, transdermal, and rectal.

The inventive compounds of formula I and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates, may be administered as a pharmaceutical composition in any suitable pharmaceutical form recognizable to the skilled artisan. Suitable pharmaceutical forms include, but are not limited to, solid, semisolid, liquid, or lyopholized formulations, such as tablets, powders, capsules, suppositories, suspensions, and aerosols. The pharmaceutical composition may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known to those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the

pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraural, and/or rectal administration.

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulphate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers may include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g. solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof) and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of 3C protease activity, by any known method of administering the dose including topical, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

A "therapeutically effective amount" is intended to mean that amount of a compound of formula I that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus. The amount of a given compound of formula I that will correspond to a "therapeutically effective amount" will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, and the identity of the mammal in need thereof, but can nevertheless be readily determined by one of skill in the art.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus, and includes:

(a) prophylactic treatment in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but not yet diagnosed as having it;

(b) inhibiting the disease condition; and/or

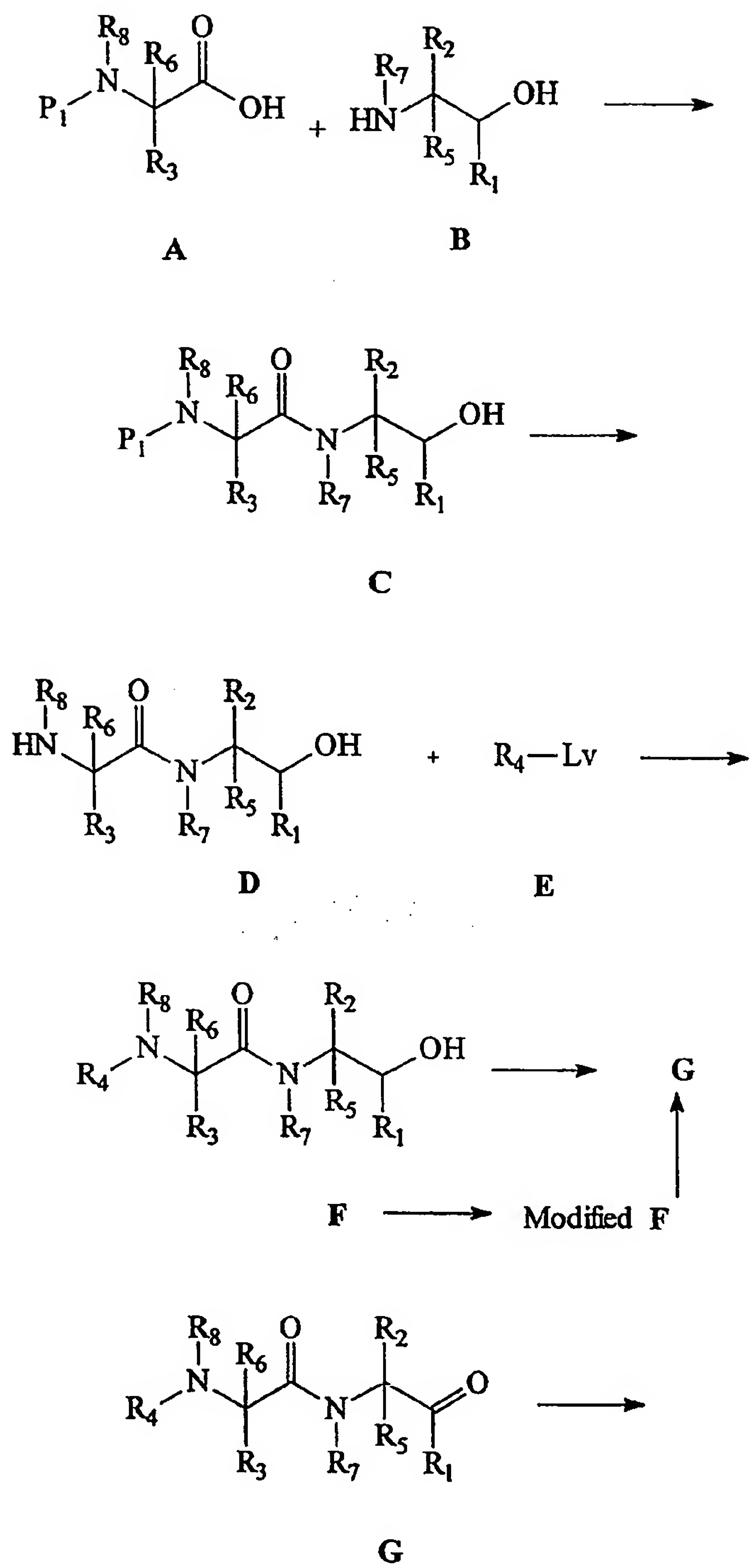
(c) alleviating, in whole or in part, the disease condition.

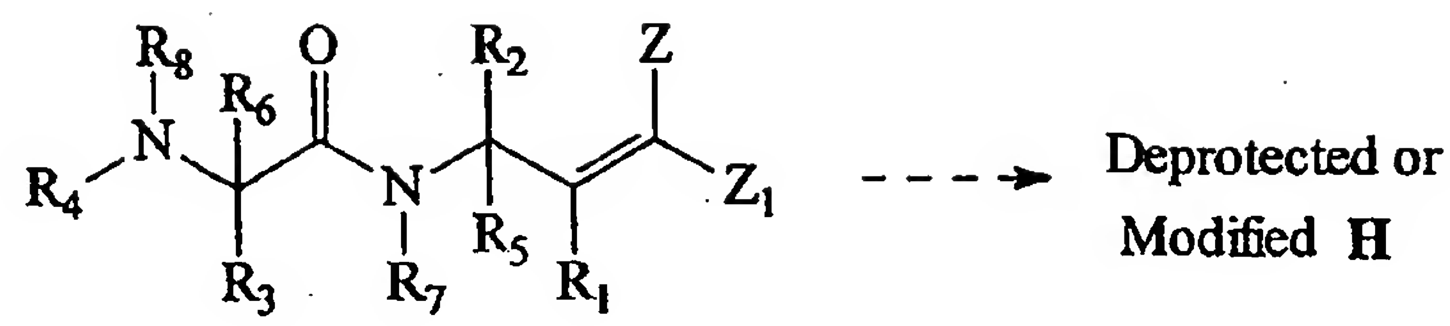
The inventive compounds, and their salts, solvates, crystal forms, active metabolites, and prodrugs, may be prepared by employing the techniques available in the

art using starting materials that are readily available. Certain novel and exemplary methods of preparing the inventive compounds are described below.

Preferably, the inventive compounds of formula I are prepared by the novel methods of the present invention, including the four general methods shown below. In each of these general methods, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, Z, and Z_1 are as defined above (for formula I).

General Method I:

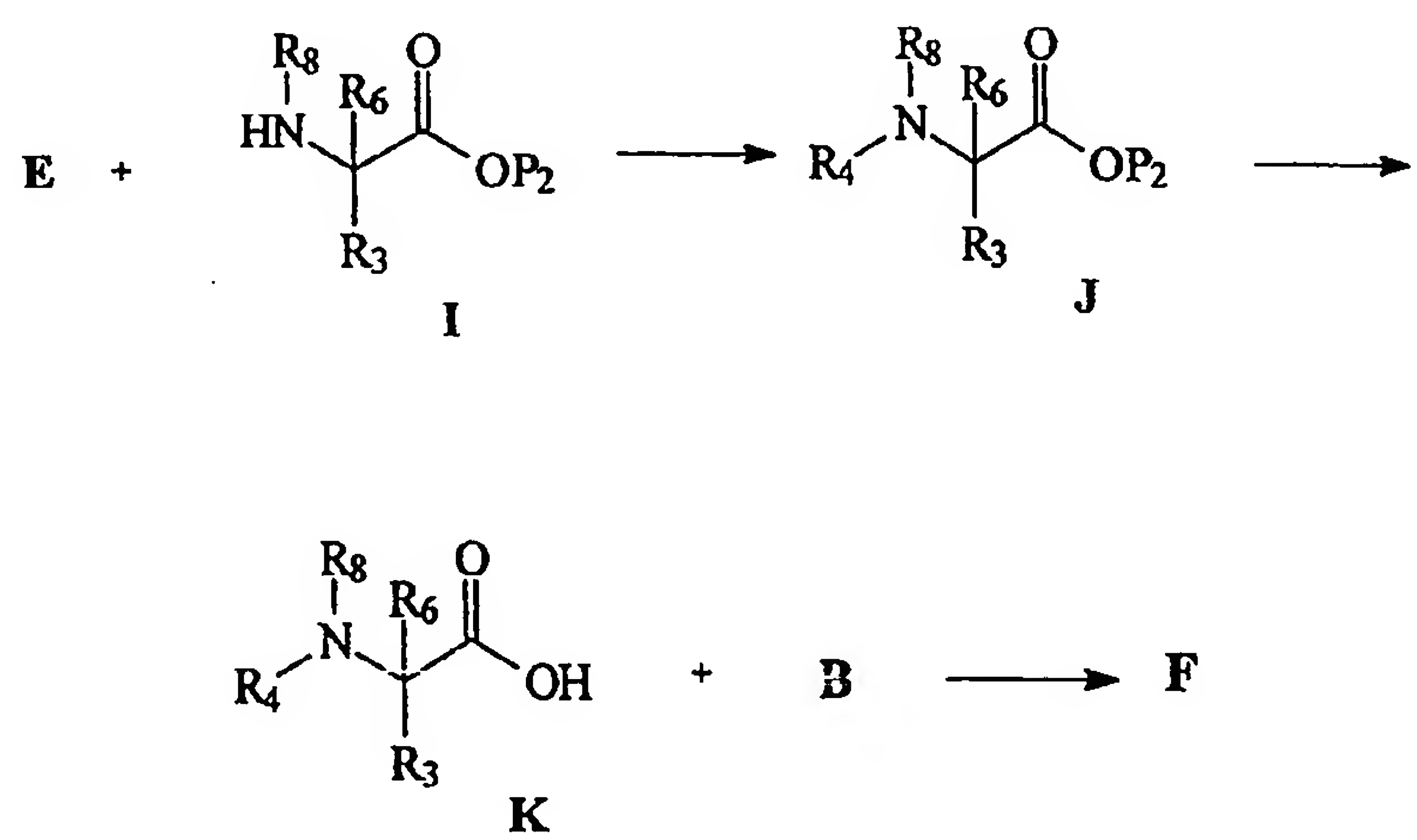




H

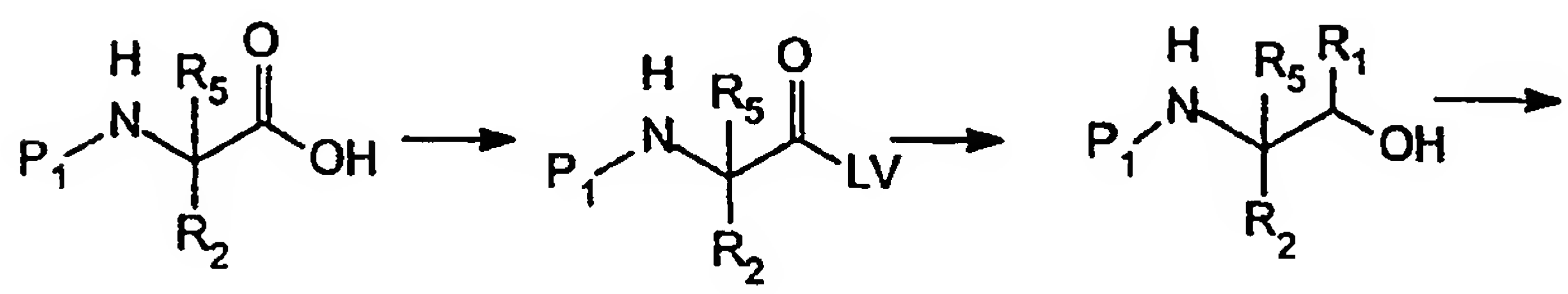
In General Method I, protected amino acid A, where P_1 is an appropriate protecting group for nitrogen, is subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to produce amide **C**. Amide **C** is then deprotected to give free amine (or salt thereof) **D**. Amine **D** and compound **E**, where "Lv" is an appropriate leaving group, are subjected to a bond forming reaction generating compound **F**. Compound **F** is oxidized to intermediate **G**, or modified at R_4 and/or R_8, to give one or more modified **F** compounds. Modified **F** compounds are oxidized to intermediate **G**. Intermediate **G** is then transformed into unsaturated product **H**. If protecting groups are used on any R groups (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

An alternative method to prepare intermediate **F** is described as follows:

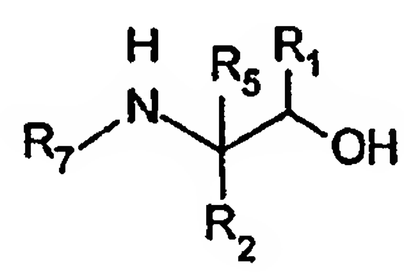


Compound **E** and amino acid (or salt thereof) **I**, where P_2 is an appropriate protecting group for oxygen, are subjected to a bond forming reaction to produce intermediate **J**. Intermediate **J** is deprotected to yield free carboxylic acid **K**, which is subsequently subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to generate intermediate **F**.

Amino alcohol **B** can be prepared as follows:



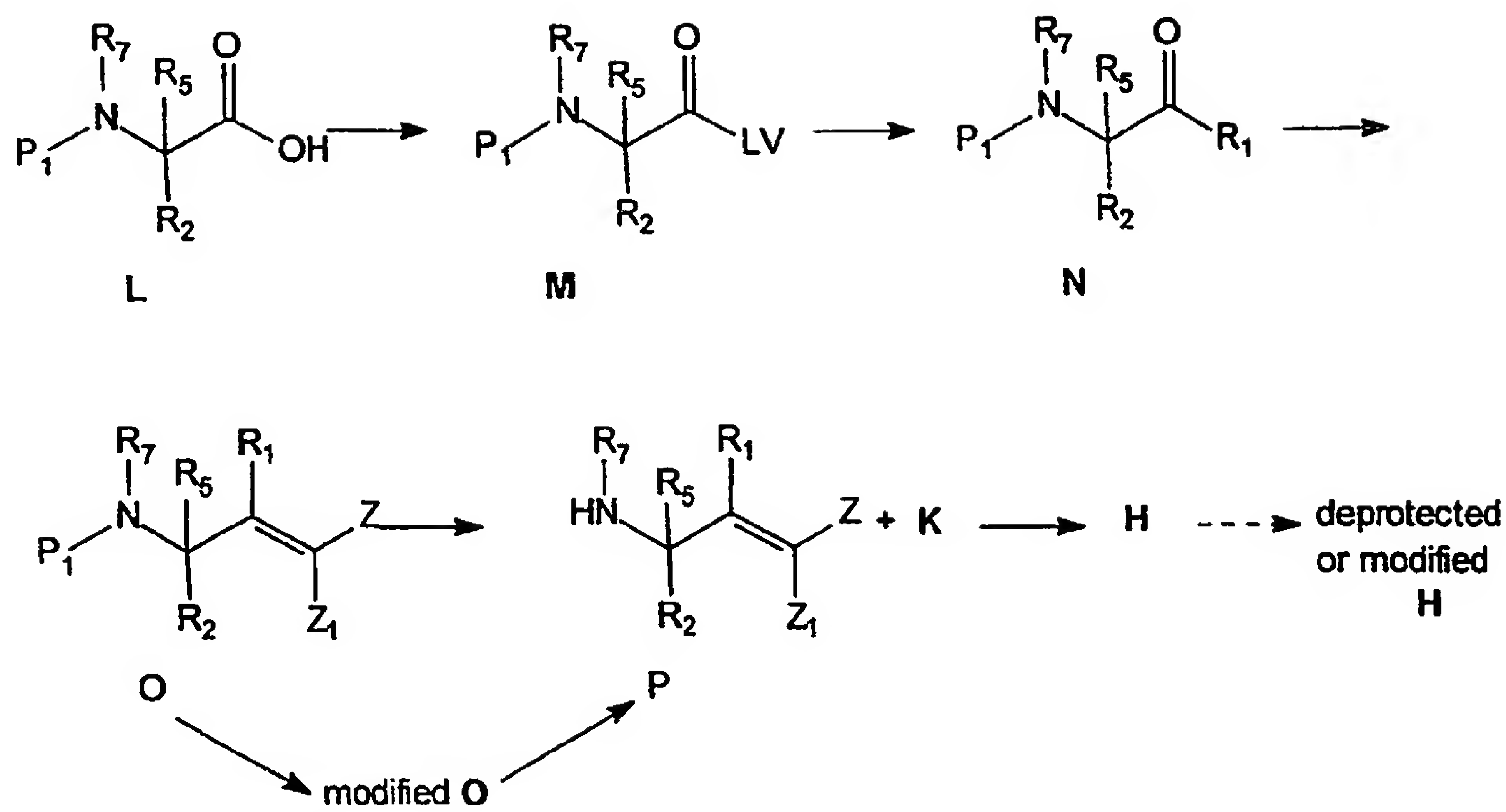
L M Q



B

Amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to carbonyl derivative **M**, where "Lv" is a leaving group. Compound **M** is subjected to a reaction where "Lv" is reduced to protected amino alcohol **Q**. Amino alcohol **Q** is deprotected to give amino alcohol **B**.

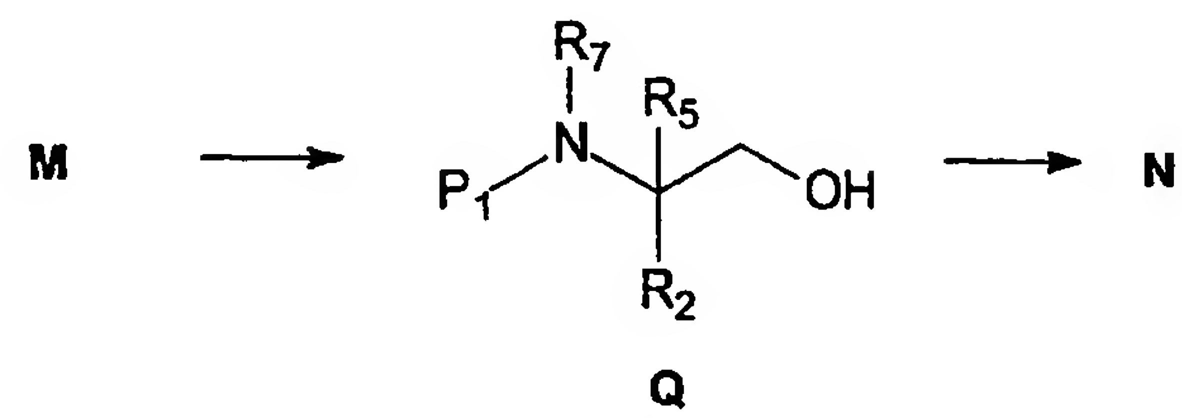
General Method **II**:



In General Method **II**, amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative **M**, where "Lv" is a leaving group. Compound **M** is subjected to a reaction where "Lv" is replaced by R_1 to give derivative **N**. Derivative **N** is then transformed into unsaturated product **O**. Unsaturated compound **O** is deprotected to give free amine (or salt thereof) **P**, or modified one or more times at R_2, R_5, R_7, Z, and/or Z_1 to give one or more modified **O** compounds.

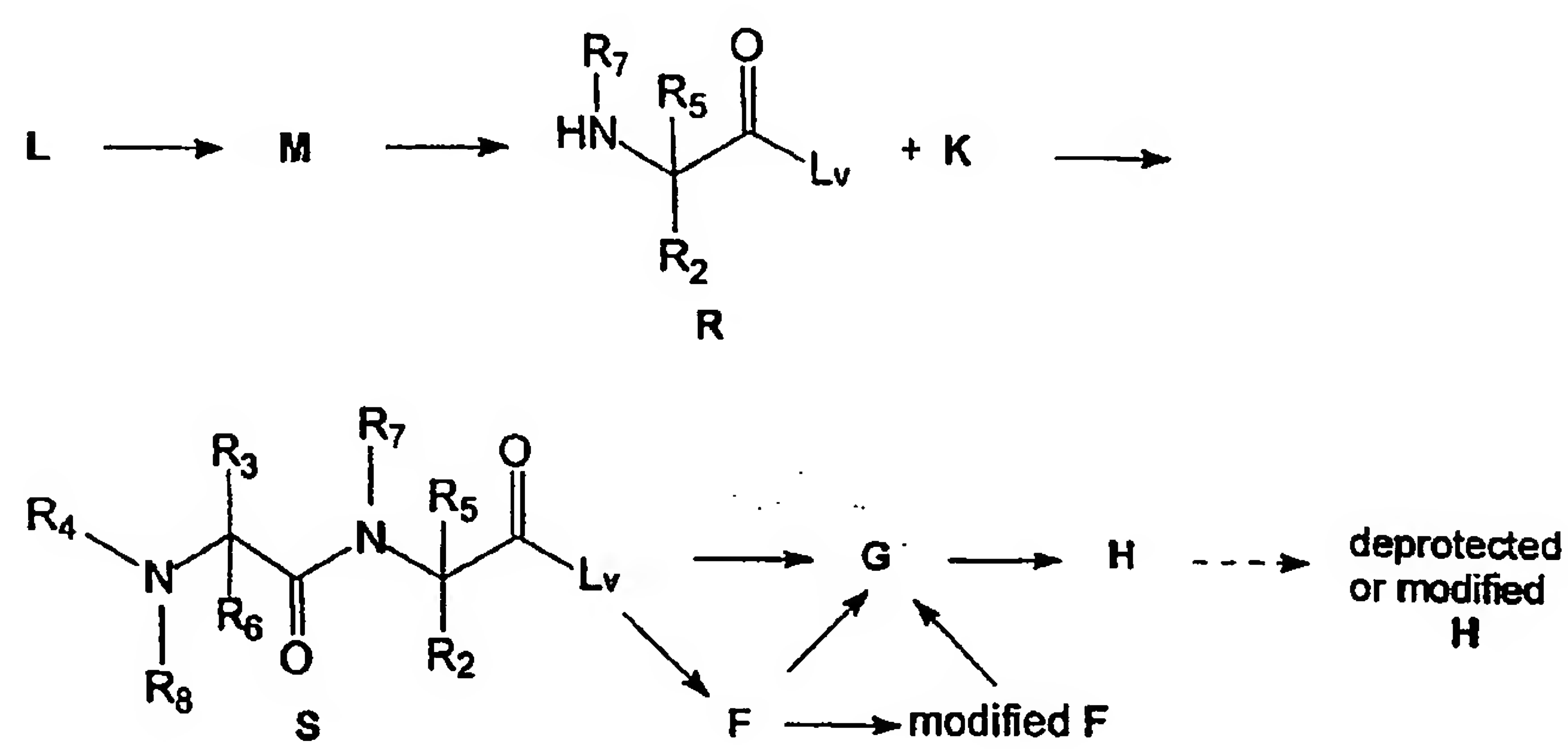
Modified **O** is then deprotected to give amine (or salt thereof) **P**. Amine **P** is subsequently subjected to an amide forming reaction with carboxylic acid **K**, prepared as described in General Method **I**, to give final product **H**. If protecting groups were used on any R group (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

An alternative method to prepare intermediate **N** is described as follows:



Compound **M** is subjected to a reaction where "Lv" is reduced to protected amino alcohol **Q**. Amino alcohol **Q** is subsequently oxidized to derivative **N**.

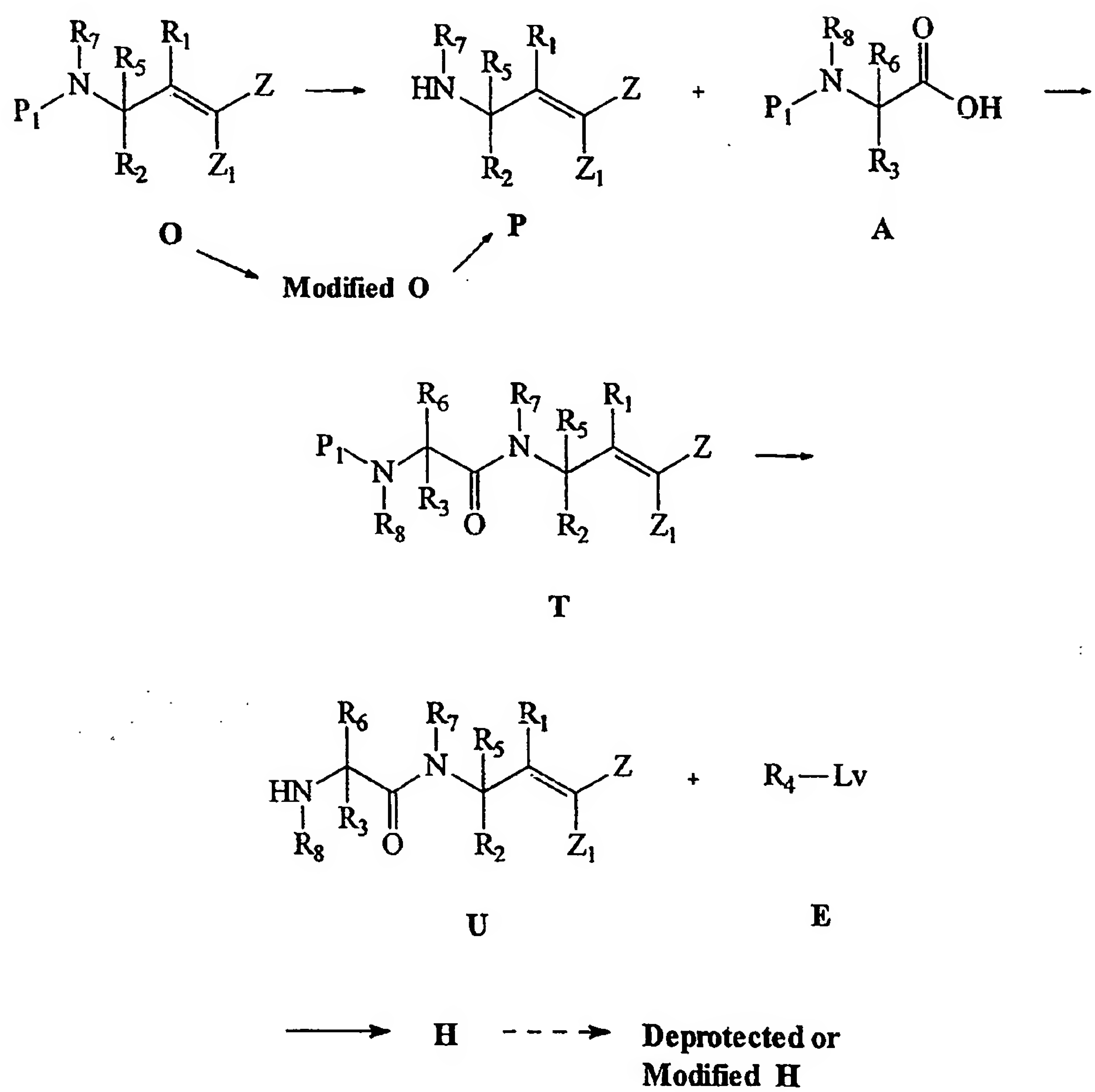
General Method **III**:



In General Method III, amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative **M**, where "Lv" is a leaving group. Derivative **M** is deprotected to give free amine (or salt thereof) **R**, which subsequently is subjected to an amide forming reaction with carboxylic acid **K** to give intermediate **S**. Intermediate **S** is then either converted directly to carbonyl intermediate **G**, or successively reduced to alcohol **F**, which is then oxidized to **G**. Intermediate **G** is subjected to a reaction to yield the unsaturated final product **H**. If protecting groups

were used on any R groups (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

General Method **IV**:

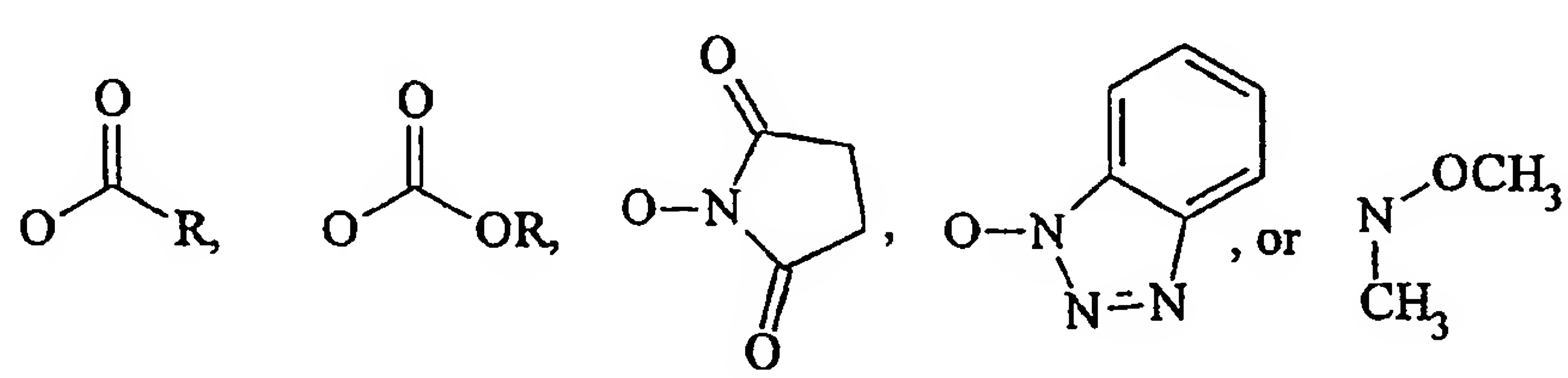


In General Method **IV**, free amine (or salt thereof) **P**, prepared from intermediate **O** as described in General Method **II**, is converted to amide **T** by reaction with amino acid **A**, where P_1 is an appropriate protecting group for nitrogen. Compound **T** is further deprotected to free amine (or salt thereof) **U**, which is subsequently converted to

H with reactive intermediate E. If protecting groups were used on any R groups (R_1-R_8) and/or on Z and/or Z_1, product H is deprotected and/or further modified to yield "deprotected or modified H."

Suitable protecting groups for nitrogen are recognizable to those skilled in the art and include, but are not limited to benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, p-methoxybenxyloxycarbonyl, trifluoroacetamide, and p-toluenesulfonyl. Suitable protecting groups for oxygen are recognizable to those skilled in the art and include, but are not limited to $-CH_3$, $-CH_2CH_3$, tBu, $-CH_2Ph$, $-CH_2CH=CH_2$, $-CH_2OCH_2CH_2Si(CH_3)_3$, and $-CH_2CCl_3$. Other examples of suitable protecting groups for nitrogen or oxygen can be found in T. Green & P. Wuts, Protective Groups in Organic Synthesis (2nd ed. 1991), which is incorporated herein by reference.

Suitable leaving groups are recognizable to those skilled in the art and include, but are not limited to, Cl, Br, I, sulfonates, O-alkyl groups,



wherein "R" is any suitable substituent, such as an alkyl group or an aryl group. Other examples of suitable leaving groups are described in J. March, Advanced Organic Chemistry, Reactions, Mechanisms, and Structure (4th ed. 1992) at pages 205, 351-56, 642-43, 647, 652-53, 666, 501, 520-21, 569, 579-80, 992-94, 999-1000, 1005, and 1008, which are incorporated herein by reference.

EXAMPLES

Proton magnetic resonance spectra (NMR) were determined using a Tech-Mag spectrometer operating at a field strength of 300 megahertz (MHZ) or Varian UNITY*plus* 300. Chemical shifts are reported in parts per million (δ) and setting the references such that in $CDCl_3$ the $CHCl_3$ is at 7.26 ppm, in CD_3OD the CH_3OH is at 4.9 ppm, in C_6D_6 the C_6H_6 is at 7.16 ppm, in acetone-d_6 the acetone is at 2.02 ppm, and in DMSO-d_6 the DMSO is at 2.49 ppm. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; bs, broad singlet; bt, broad triplet; m, multiplet. Mass spectra (FAB; fast atom bombardment) were determined at the Scripps Research Institute Mass Spectometry Facility, San Diego, CA. Infrared absorption (IR) spectra were taken on a MIDAC Corporation FTIR or a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc. Norcross, Georgia and gave results for the elements stated with ± 0.4% of the theoretical values. Flash chromatography was performed using Silica gel 60 (Merck Art 9385). Thin layer chromatographs ("TLC") were performed on precoated sheets of silica 60 F_{254} (Merck Art 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Anhydrous *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethysulfoxide (DMSO), were used as is. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. "Et_2O" refers to diethyl ether. "Pet. ether" refers to petroleum ether with a boiling range of 36-53 °C. "TFA" refers to trifluoroacetic acid. "Et_3N" refers to triethylamine. Other abbreviations include: methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), acetyl (Ac), methyl (Me), triphenylmethyl (Tr),

benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (BOC), *m*-chloroperoxybenzoic acid (*m*-CPBA), alanine (Ala), glutamine (Gln), proline (Pro), leucine (Leu), methionine (Met), phenylalanine (Phe), and homophenylalanine (hPhe), where "L" represents natural amino acids and "D" unnatural amino acids. "DL" represents racemic mixtures. A simplified naming system was used to identify intermediates and final products: Amino acid and peptide alcohols are given the suffix 'ol' (for example "methionol"). Amino acid and peptide aldehydes are given the suffix 'al' (for example "methional"). When naming final products, italicized amino acid abbreviations represent modifications at the C-terminus of that residue where the following apply:

1. acrylic acid esters are reported as either "E" (trans) or "Z" (cis) propenoates.
2. lactones 6, 8, 10, and 12 are reported as E-α-vinyl-γ-butyrolactones.
3. acrylamides are reported as either E or Z propenamides except in the case of compound 7, which is reported as 1-(2',3'-Dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone and compound 26, which is reported as 1-[1',2'-oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-propenone.
4. acryloxazolidone 17 is reported as 1-[2'-oxazolidon-3'-yl]-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-propenone.

<u>Example 1 - Preparation of Compound 1: Ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-Propenoate.</u>

Preparation of Intermediate BOC-L-(Tr-Gln)-N(OMe)Me.

Isobutyl chloroformate (4.77 mL, 36.8 mmol, 1.0 equiv) was added to a solution of BOC-L-(Tr-Gln) (18.7 g, 36.7 mmol, 1 equiv) and 4-methylmorpholine (8.08 mL, 73.5 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, then *N,O*-dimethylhydroxylamine hydrochloride (3.60 g, 36.7 mmol, 1.0 equiv) was added. The resulting solution was stirred at 0 °C for 20 min and at 23 °C for 2 h, and then it was partitioned between water (150 mL) and CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (gradient elution, 20-40% hexanes in EtOAc) provided BOC-L-(Tr-Gln)-N(OMe)Me (16.1 g, 82%) as a white foam: IR (KBr) 3411, 3329, 3062, 1701, 1659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.63-1.77 (m, 1 H), 2.06-2.17 (m, 1 H), 2.29-2.43 (m, 2 H), 3.17 (s, 3 H), 3.64 (s, 3 H), 4.73 (s, bs, 1 H), 5.38-5.41 (m, 1 H), 7.20-7.31 (m, 15 H); Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

Preparation of Intermediate BOC-L-(Tr-Glutaminal).

Diisobutylaluminum hydride (50.5 mL of a 1.5 M solution in toluene, 75.8 mmol, 2.5 equiv) was added to a solution of [BOC-L-(Tr-Gln)]-N(OMe)Me (16.1 g, 30.3 mmol, 1 equiv) in THF at -78 °C, and the reaction mixture was stirred at -78 °C for 4 h. Methanol (4 mL) and 1.0 M HCl (10 mL) were added sequentially, and the mixture was warmed to 23 °C. The resulting suspension was diluted with Et_2O (150 mL) and was washed with 1.0 M HCl (3 x 100 mL), half-saturated $NaHCO_3$ (100 mL), and water (100 mL). The organic

layer was dried over $MgSO_4$, filtered, and was concentrated to give crude BOC-L-(Tr-Glutaminal) (13.8 g, 97%) as a white solid: mp = 114-116 °C; IR (KBr) 3313, 1697, 1494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.65-1.75 (m, 1 H), 2.17-2.23 (m, 1 H), 2.31-2.54 (m, 2 H), 4.11 (bs, 1 H), 5.38-5.40 (m, 1 H), 7.11 (s, 1 H), 7.16-7.36 (m, 15 H), 9.45 (s, 1 H).

Preparation of Intermediate Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenoate.

Sodium bis(trimethylsilyl)amide (22.9 mL of a 1.0 M solution in THF, 22.9 mmol, 1.0 equiv) was added to a solution of triethyl phosphonoacetate (5.59 g, 22.9 mmol, 1.0 equiv) in THF (200 mL) at -78 °C, and the resulting solution was stirred for 20 min at that temperature. Crude [BOC-L-(Tr-Glutaminal)]-H (10.8 g, 22.9 mmol, 1 equiv) in THF (50 mL) was added via cannula, and the reaction mixture was stirred for 2 h at -78 °C, warmed to 0 °C for 10 min, and partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) provided ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (10.9 g, 88%) as a white foam: IR (thin film) 3321, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.2), 1.42 (s, 9 H), 1.70-1.78 (m, 1 H), 1.80-1.96 (m, 1 H), 2.35 (t, 2 H, J = 7.0), 4.18 (q, 2 H, J = 7.2), 4.29 (bs, 1 H), 4.82-4.84 (m, 1 H), 5.88 (dd, 1 H, J = 15.7, 1.6), 6.79 (dd, 1 H, J = 15.7, 5.3), 6.92 (s, 1 H), 7.19-7.34 (m, 15 H); Anal. ($C_{33}H_{38}N_2O_5$) C, H, N.

Preparation of Intermediate Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenoate (0.751 g, 1.38 mmol) was dissolved in 1,4-dioxane (5 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 5 mL) was added dropwise. The reaction solution was stirred for 2 h and then the solvent was evaporated to provide the amine salt as a foam which was used without purification. The crude amine salt was dissolved in dry CH_2Cl_2 (12 mL) under argon. 4-Methylmorpholine (1.05 mL, 9.55 mmol), hydroxybenzotriazole hydrate (0.280 g, 2.07 mmol), BOC-L-N-Me-Phe (0.386 g, 1.38 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.397 g, 2.07 mmol) were added successively. The reaction mixture was stirred overnight and poured into water (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (25% acetone in hexanes, then 3% MeOH in CH_2Cl_2) to provide ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate (0.450 g, 46%) as a foam: IR (thin film) 3318, 1708, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer) δ 1.28 (t, 3H, J = 7.2 Hz), 1.37 (s, 9H), 1.63-1.87 (m, 1H), 1.94-2.06 (m, 1H), 2.26-2.37 (m, 2H), 2.66 (s, 3H), 3.00 (dd, 1H, J = 13.5, 9.2 Hz), 3.29 (dd, 1H, J = 13.5, 6.4 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.51-4.70 (m, 2H), 5.71 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 8.1 Hz), 6.73 (dd, 1H, J = 15.6, 4.8 Hz), 6.97 (s, 1H), 7.12-7.36 (m, 20H); Anal. ($C_{43}H_{49}N_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.433 g, 0.615 mmol) was dissolved in 1,4-dioxane (2.5 mL) and treated dropwise with a solution of hydrogen chloride in 1,4-dioxane (4.0 *M*, 2.5 mL). After stirring for 2 hours, the solvent was

evaporated to provide ethyl-3-[L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate hydrochloride which was used without purification. One half of the crude amine salt formed was dissolved in dry CH_2Cl_2 (3 mL). 4-Methylmorpholine (0.169 mL, 1.54 mmol) and benzyl chloroformate (0.088 mL, 0.62 mmol) were added sequentially. After stirring overnight, the solvent was evaporated. The residue was purified by chromatography (20% to 25% acetone in hexanes) to provide ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.112 g, 49%) as a foam: IR (thin film) 3316, 1708, 1684, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer) δ 1.29 (t, 3H, J = 7.2 Hz), 1.59-1.72 (m, 1H), 1.82-2.01 (m, 1H), 2.19-2.26 (m, 2H), 2.73 (s, 3H), 2.99 (dd, 1H, J = 14.2, 9.2 Hz), 3.29 (dd, 1H, J = 14.2, 6.8 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.48-4.60 (m, 1H), 4.66 (dd, 1H, J = 9.2, 6.8 Hz), 4.93 (d, 1H, J = 12.3 Hz), 5.02 (d, 1H, J = 12.3 Hz), 5.71 (dd, 1H, J = 15.6, 1.6 Hz), 6.48 (d, 1H, J = 8.1 Hz), 6.70 (dd, 1H, J = 15.6, 5.4 Hz), 6.87 (s, 1H), 7.05-7.37 (m, 25H); Anal. ($C_{46}H_{47}N_3O_6$•0.5 H_2O) C, H, N.

Preparation of Product - Ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.096 g, 0.13 mmol) was dissolved in dry CH_2Cl_2 (4 mL). Triisopropylsilane (0.077 mL, 0.376 mmol) and trifluoroacetic acid (2 mL) were added sequentially to give a bright yellow solution. After stirring for 30 min, no yellow color remained. The solvents were evaporated to give a semi-solid residue which was purified by chromatography (5% methanol in CH_2Cl_2) to provide ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)- E-propenoate (0.061 g, 95%) as a colorless glass: IR (thin film) 3412, 3336, 3213, 1696, 1684, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) (major isomer) δ 1.28 (t, 3H, J = 7.2 Hz), 1.63-2.03 (m, 2H), 2.11-2.18 (m, 2H), 2.88 (s, 3H), 3.05

(dd, 1H, J= 14.0, 9.3 Hz), 3.31 (dd, 1H, J = 14.0, 6.8 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.51-4.63 (m, 1H), 4.71-4.80 (m, 1H), 4.95-5.16 (m, 2H), 5.73 (d, 1H, J = 15.9 Hz), 5.77-5.92 (m, 1H), 6.10 (s, 1H), 6.65-6.78 (m, 2H), 7.09-7.38 (m, 10H); Anal. ($C_{27}H_{33}N_3O_6$•0.75 H_2O) C, H, N.

Example 2 - Preparation of Compound 2: Ethyl-3-(CBZ-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.216 g, 0.308 mmol) was deprotected and coupled with CBZ-L-Leu (0.082 g, 0.309 mmol) using the procedure described for the formation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after two chromatographies (30% acetone/hexanes, then 2% methanol/CH_2Cl_2) as a glass (0.095 g, 36%): IR (thin film) 3304, 1708, 1659 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.63 (d, 3H, J = 6.7 Hz), 0.66 (d, 3H, J = 6.8 Hz), 0.83-0.89 (m, 6H), 1.12-1.48 (m, 4H), 1.26 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.51-1.66 (m, 2H), 1.69-1.80 (m, 1H), 1.88-2.04 (m, 2H), 2.16-2.32 (m, 4H), 2.90 (s, 6H), 2.95-3.17 (m, 2H), 3.25 (dd, 1H, J = 14.6, 3.4 Hz), 3.37 (dd, 1H, J = 13.7, 6.5 Hz), 4.11-4.25 (m, 2H), 4.17 (q, 4H, J = 7.2 Hz), 4.38-4.51 (m, 2H), 4.53-4.67 (m, 3H), 4.85-5.16 (m, 7H), 5.72 (d, 1H, J = 15.9 Hz), 5.95 (dd, 1H, J = 15.9, 1.2 Hz), 6.43 (d, 1H, J = 8.4 Hz), 6.74 (dd, 1H, J = 15.9, 5.3 Hz), 6.80 (s, 1H), 6.84 (dd, 1H, J = 15.9, 6.5 Hz), 7.09-7.38 (m, 50H), 8.00 (d, 1H, J = 7.8 Hz); Anal. ($C_{52}H_{58}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Product - Ethyl-3-(CBZ-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.056 g, 0.066 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-*Gln*]-E-propenoate (after chromatography, 5% MeOH in CH_2Cl_2) as a glass (0.029 g, 73%): IR (thin film) 3401, 3298, 3225, 1678, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.62-0.69 (m, 6H), 0.87-0.94 (m, 6H), 1.15-1.32 (m, 8H), 1.37-1.49 (m, 2H), 1.61-1.86 (m, 4H), 1.90-2.03 (m, 2H), 2.10-2.20 (m, 4H), 2.93 (s, 3H), 2.95 (s, 3H), 2.97-3.11 (m, 1H), 3.17-3.28 (m, 2H), 3.41-3.49 (m, 1H), 4.16-4.29 (m, 5H), 4.42-4.52 (m, 2H), 4.55-4.71 (m, 3H), 4.95-5.12 (m, 4H), 5.39-5.52 (m, 4H), 5.78 (d, 1H, J = 15.9 Hz), 5.89 (s, 1H), 6.00 (dd, 1H, J = 15.9, 1.2 Hz), 6.08 (s, 1H), 6.73-6.91 (m, 3H), 7.12-7.37 (m, 20H), 7.98 (d, 1H, J = 8.1 Hz); Anal. ($C_{33}H_{44}N_4O_7$•0.5 H_2O) C, H, N.

Example 3 - Preparation of Compound 3: Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-Propenoate.

Preparation of Intermediate
Ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.545 g, 1.00 mmol) was deprotected and coupled with the dicyclohexylamine salt of BOC-L-N-Me-(OMe)-Tyr (0.630 g, 1.28 mmol) using the procedure described in Example 1 for the formation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (after chromatography, 33% EtOAc in hexanes) as a white foam (0.380 g, 52%): IR (thin film) 3307, 1708, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 1.38 (s, 9H), 1.60-1.77 (m, 1H), 1.94-2.07 (m,

1H), 2.27-2.36 (m, 2H), 2.67 (s, 3H), 2.89-2.99 (m, 1H), 3.18-3.27 (m, 1H), 3.78 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 4.44-4.65 (m, 2H), 5.73 (d, 1H, J = 15.6 Hz), 6.35 (d, 1H, J = 8.7 Hz), 6.69-6.84 (m, 3H), 6.94 (s, 1H), 7.04-7.12 (m, 2H), 7.17-7.34 (m, 15H); Anal. ($C_{44}H_{51}N_3O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (0.360 g, 0.491 mmol) was dissolved in 1,4-dioxane (2 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 2 mL) was added dropwise. The reaction solution was stirred for 2 h, and then the solvent was evaporated to provide the amine salt as a foam which was used without purification. The crude amine salt was dissolved in dry CH_2Cl_2 (12 mL) under argon. 4-Methylmorpholine (0.208 mL, 1.89 mmol), CBZ-L-Leu (0.125 g, 0.471 mmol), hydroxybenzotriazole hydrate (0.096 g, 0.71 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.136 g, 0.709 mmol) were added successively. After stirring overnight, 4-methylmorpholine (0.208 mL, 1.89 mmol), hydroxybenzotriazole hydrate (0.096 g, 0.71 mmol), CBZ-L-Leu (0.125 g, 0.471 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.136 g, 0.709 mmol) were added again. Then 4-dimethylaminopyridine (0.010 g, 0.082 mmol) was added. After stirring 48 h more, the reaction mixture was poured into water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3x 75 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (38% to 50% EtOAc in hexanes) to provide

ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]- E-propenoate (0.210 g, 51%) as a colorless glass: IR (thin film) 3295, 1708, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.65 (d, *J* = 6.5 Hz), 0.68 (d, *J* = 6.8 Hz), 0.82-0.91 (m), 1.14-1.50 (m), 1.52-1.66 (m), 1.68-1.81 (m), 1.87-2.02 (m), 2.16-2.28 (m), 2.89 (s), 2.92 (s), 2.95-3.09 (m), 3.14-3.23 (m), 3.24-3.33 (m), 3.76 (s), 3.76 (s), 4.08-4.25 (m), 4.41-4.49 (m), 4.54-4.63 (m), 4.83-5.16 (m), 5.73 (d, *J* = 15.6 Hz), 5.95 (dd, *J* = 15.7, 1.1 Hz), 6.40 (d, *J* = 8.4 Hz), 6.74 (dd, *J* = 15.6, 5.0 Hz), 6.78-6.87 (m), 6.99-7.06 (m), 7.16-7.34 (m), 7.97 (d, *J* = 7.8 Hz); Anal. ($C_{53}H_{60}N_4O_8$•0.5 H_2O) C, H, N.

Preparation of Product -
Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (0.128 g, 0.145 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-propenoate (after chromatography, 5% MeOH in CH_2Cl_2) as a colorless glass (0.083 g, 89%): IR (thin film) 3401, 3295, 3201, 1708, 1666, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.64-0.71 (m), 0.87-0.94 (m), 1.27 (t, *J* = 7.2 Hz), 1.28 (t, *J* = 7.2 Hz), 1.38-1.51 (m), 1.61-1.85 (m), 1.87-2.02 (m), 2.07-2.21 (m), 2.80-2.92 (m), 2.94 (s), 2.96 (s), 2.97-3.06 (m), 3.08-3.21 (m), 3.36 (dd, *J* = 14.0, 6.2 Hz), 3.76 (s), 4.16-4.28 (m), 4.18 (q, *J* = 7.2 Hz), 4.45-4.66 (m), 4.94-5.12 (m), 5.52 (d, *J* = 7.8 Hz), 5.58 (d, *J* = 7.8 Hz), 5.69 (s), 5.77 (d, *J* = 15.9 Hz), 5.99 (s), 6.00 (dd, *J* = 15.9, 1.2 Hz), 6.21 (s), 6.76 (dd, *J* = 15.9, 5.3 Hz), 6.79-6.91 (m), 7.02-7.10 (m), 7.26-7.37 (m), 7.97 (d, *J* = 8.1 Hz); ($C_{34}H_{46}N_4O_8$•0.5 H_2O) C, H, N.

Example 4 - Preparation of Compound 5: Ethyl-3-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Cyclopentyl Chlorothiolformate.

Cyclopentanethiol (10.7 mL, 0.1 mol) was dissolved in 200 mL of CH_2Cl_2. Triphosgene (11.13 g, 37.5 mmol) was added, and the reaction mixture was cooled to 0 °C. Et_3N (14.1 mL, 0.1 mol) was added dropwise, and the reaction was allowed to warm to room temperature over a period of one hour. The solvent was carefully removed under reduced pressure at 20 °C due to the volatility of the product. The resulting residue was taken up in Et_2O, and the solids were filtered and washed with more Et_2O. The solvent was again carefully removed under reduced pressure, and the product was purified by distillation (85% yield): colorless liquid (bp 70-74 °C; 1 torr): IR(neat) 1756, 830 cm^{-1}; ^1H NMR (benzene-d_6) δ 1.01-1.23 (m, 6H), 1.49-1.60 (m, 2H), 3.20-3.29 (m, 1H).

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-OBn.

The p-toluenesulfonic acid salt of L-Leu-OBn (3.14 g, 8.0 mmol) was dissolved in 70 mL of CH_2Cl_2, followed by 2.25 mL (16 mmol) of Et_3N. Cyclopentyl chlorothiolformate (1.32 g, 8.0 mmol) was dissolved in 10 mL of CH_2Cl_2 and added dropwise to the reaction. The reaction was stirred one hour, and the solvent was removed in vacuo. The product was purified by flash silica gel chromatography eluting with 5% EtOAc/ hexanes to give 2.48 g (71%) of a clear oil; IR(KBr) 3318, 2959, 2870, 1744, 1649, 1516, 1186, 854, 746, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.82 (d, 3H, J = 6.0 Hz), 0.86 (d, 3H, J = 6.0 Hz), 1.39-1.70 (m, 9H), 1.97 (m, 2H), 3.55 (quint, 1H, J = 7.0 Hz), 4.23 (m,

1H), 5.09 (d, 1H, J = 12.5 Hz), 5.13 (d, 1H, J = 12.5 Hz), 7.35 (m, 5H), 8.48 (d, 1H, J = 7.7 Hz). Anal. ($C_{19}H_{27}NO_3S$) C, H, N.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu.

Cyclopentylthiocarbonyl-L-Leu-OBn (2.42 g, 6.92 mmol) was dissolved in 35 mL of CH_2Cl_2, followed by 4.51 mL (41.5 mmol) of anisole. The reaction was cooled to 0 °C, and $AlCl_3$ (2.88 g, 21.6 mmol), dissolved in 35 mL of nitromethane, was added dropwise via pipet. The ice bath was removed, and the reaction was allowed to stir at rt for 5 h. The reaction was diluted with EtOAc and washed with 10% HCl. The organic phase was washed with a sat. $NaHCO_3$ solution. The basic solution was then reacidified to a pH = 1 with 10% HCl, and the product was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 0.23 g (93%) of an opaque oil: IR(neat) 3302-2473 (bs), 1715, 1652, 1532, 1202, 925, 852, 673, 563 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.82 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.40-1.70 (m, 9H), 1.98 (m, 2H), 3.53 (quint, 1H, J = 7.0 Hz), 4.18 (m, 1H), 8.29 (d, 1H, J = 8.0 Hz), 12.58 (bs). Anal. ($C_{12}H_{21}NO_3S$) C, H, N.

Preparation of Intermediate CBZ-L-(Tr-Gln).

CBZ-L-Gln (28.03 g, 100 mmol) was dissolved in 300 mL of glacial acetic acid. To this solution was added triphenylmethanol (26.83 g, 100 mmol), acetic anhydride (18.87 mL, 200 mmol), and 0.5 mL of conc. sulfuric acid. The reaction was heated to 55 °C and stirred for one hour. After cooling to room temperature, the mixture was concentrated under reduced pressure to one-third the original volume. Ice water was added, and the

product extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was recrystallized from CH_2Cl_2/hexane, and the resulting crystals washed with Et_2O, yielding 37.27 g (71%) as a white solid: IR (KBr) 3418, 3295, 3059, 3032, 2949, 2515, 1699, 1628, 1539, 1504, 1447, 1418, 1341, 1242, 1209, 1061, 748, 696 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.71 (m, 1 H), 1.88 (m, 1 H), 2.38 (m, 2 H), 3.97 (m, 1 H), 5.04 (s, 2 H), 7.14-7.35 (m, 20H), 7.52 (d, 1 H, J = 7.7 Hz), 8.60 (s, 1 H).

Preparation of Intermediate CBZ-L-(Tr-Gln)OMe.

CBZ-L-(Tr-Gln) (0.26 g, 0.5 mmol) was added to a stirring solution of 0.25 mL of acetyl chloride in 5 mL of MeOH, and stirring was continued at room temperature for 1 h. The solvent was removed in vacuo, and the residue dissolved in 100 mL CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$, and brine, followed by drying over Na_2SO_4. The crude product was purified on a short flash silica gel column, eluting with 20% EtOAc/hexane. The product (0.23 g, 84%) was obtained as a white solid: IR (KBr) 3405, 3277, 3057, 3034, 2953, 1724, 1643, 1532, 1493, 1447, 1207, 1042, 750, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, 1 H, J = 7.0 Hz), 1.77 (m, 1 H), 1.97 (m, 1H), 3.61 (s, 3H), 4.99 (m, 1H), 5.03 (s, 2H), 7.02-7.55 (m, 20H), 7.69 (d, 1H, J = 7.7 Hz), 8.59 (s, 1H). Anal. ($C_{33}H_{32}N_2O_5$) C, H, N.

Preparation of Intermediate CBZ-L-(Tr-Glutaminol).

CBZ-L-(Tr-Gln)OMe (1.50 g, 2.79 mmol) was dissolved in 20 mL of THF and 10 mL of EtOH. LiCl (0.24 g, 5.6 mmol) was added, and the mixture stirred for 10 minutes

until all solids had dissolved. $NaBH_4$ (0.21 g, 5.6 mmol) was added, and the reaction was stirred overnight at room temperature. The solvents were removed in vacuo, the residue taken up in water, and the pH was adjusted to 2-3 with 10% HCl. The product was extracted with EtOAc, and the organic layer was washed with water and brine before drying over $MgSO_4$. The crude product was purified on a short flash silica gel column, eluting with an increasing gradient of EtOAc/benzene, yielding 1.02 g (72%) of a white glassy solid: IR (KBr) 3408, 3318, 3057, 3032, 2947, 1699, 1674, 1516, 1447, 1240, 1059, 752, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (m, 1H), 1.72 (m, 1H), 2.26 (m, 2H), 3.17-3.50 (m, 3H), 4.64 (t, 1H, J = 5.0 Hz), 5.00 (s, 2H), 7.00-7.40 (m, 20H), 6.96 (d, 1H, J = 8.5 Hz), 8.54 (s, 1H). Anal. ($C_{32}H_{32}N_2O_4$) C, H, N.

Preparation of Intermediate L-(Tr-Glutaminol).

10% Pd on carbon (0.03 g) was added to a solution of CBZ-L-(Tr-Glutaminol) (0.51 g, 1.0 mmol) in 20 mL MeOH, with stirring, and under an argon atmosphere. The reaction vessel was evacuated under vacuum and then put under an atmosphere of hydrogen using a balloon. The mixture was stirred for 4 h. At this time the hydrogen gas was evacuated and the catalyst was removed by filtration. The solvent was removed under vacuum to give a white solid in 98% yield which was used without further purification: IR (KBr) 3255, 3057, 3016, 2916, 1642, 1527, 1491, 1446, 1057, 1036, 750, 700, 636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29 (m, 1H), 1.53 (m, 1H), 2.29 (m, 2H), 3.08 (m, 1H), 3.18 (m, 2H), 3.38 (bs, 2H), 4.43 (bs, 1H), 7.14-7.28 (m, 15H), 8.62 (s, 1H). Anal. ($C_{24}H_{26}N_2O_2$) C, H, N.

Preparation of Intermediate CBZ-L-N-Me-Phe-L-(Tr-Glutaminol).

CBZ-N-Me-L-Phe (2.24 g, 7.14 mmol) was dissolved in 70 mL of THF. Carbonyldiimidazole (1.16 g, 7.14 mmol) was added, and the reaction was stirred for one hour at rt. L-(Tr-Glutaminol) (2.80 g, 7.5 mmol) was added, and the reaction was stirred overnight. At this time the solvent was removed in vacuo, and the product was purified by column chromatography on silica gel using a gradient solvent system (0-2% MeOH/$CHCl_3$) to give 3.37 g (70%) of a white amorphous solid: IR(KBr) 3304, 3057, 3028, 2949, 1668, 1495, 1447, 1142, 750, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.51 (m, 1H), 1.73 (m, 1H), 2.23 (m, 2H), 2.79 (s, 3H), 2.84 (m, 1H), 3.29 (m, 3H), 3.70 (m, 1H), 4.66 (m, 1H), 4.88 (m, 3H), 7.15-7.28 (m, 25H), 7.69 (m, 1H), 8.55 (m, 1H). MS calcd for $C_{42}H_{43}N_3O_5$+H 670, found 670.

Preparation of Intermediate L-N-Me-Phe-L-(Tr-Glutaminol).

CBZ-L-N-Me-Phe-L-(Tr-glutaminol) (3.33 g, 4.97 mmol) was dissolved in 35 mL of MeOH. The reaction was placed under slight vacuum, and then under an argon atmosphere. With care, 10% Pd/C (0.33 g) was added. The flask was purged of argon which was replaced by hydrogen gas using a balloon. The reaction mixture was stirred at room temperature for 4.5 h, at which time the flask was purged of hydrogen and the catalyst was filtered off. Solvent was removed in vacuo to give 2.36 g (89%) of a white amorphous solid: IR(KBr) 3302, 3057, 3024, 2937, 1655, 1522, 1493, 1447, 750, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (m, 1H), 1.67 (m, 1H), 2.13 (m, 1H), 2.16 (s, 3H), 2.24 (m, 1H), 2.68 (dd, 1H, J = 13.5, 7.3 Hz), 2.82 (dd, 1H, J = 13.5, 5.8 Hz), 3.10

(m, 2H), 3.25 (m, 1H), 3.67 (m, 1H), 4.63 (t, 1H, J = 5.5 Hz), 7.13-7.28 (m, 21H), 7.54 (d, 1H, J = 8.8 Hz), 8.54 (s, 1H). Anal. ($C_{34}H_{37}N_3O_3$) C, H, N.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminol).

This preparation was carried out following the procedure of L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397, the disclosure of which is entirely incorporated herein by reference. Cyclopentylthiocarbonyl-L-Leu (0.27 g, 1.05 mmol) was dissolved in 3.5 mL of DMF. Diisopropylethylamine (0.37 mL, 2.10 mmol) was added, followed by 0.56 g (1.05 mmol) of L-N-Me-Phe-L-(Tr-glutaminol). The reaction was cooled to 0 °C and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.398 g, 1.05 mmol) was added. The reaction mixture was allowed to warm to room temperature whereupon the DMF was removed in vacuo. The residue was dissolved with EtOAc, and the organic phase washed consecutively with 10% HCl solution, saturated $NaHCO_3$ solution, H_2O, and brine. The solvent was dried ($MgSO_4$), filtered, and concentrated to give a residue which was subjected to flash column chromatography on silica gel (gradient; 0-1% MeOH/$CHCl_3$) to give 0.49 g (60%) of a white amorphous solid: IR(KBr) 3293, 3057, 3024, 2955, 2868, 1634, 1493, 1447, 1205, 752, 700 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.18 (m), 0.62 (m), 0.79 (d, J = 6.3 Hz), 1.00-2.05 (m), 2.08-2.40 (m), 2.81 (s), 2.88 (m), 2.95 (s), 3.05-3.53 (m), 3.65 (m), 3.79 (m), 4.27 (m), 4.61 (m), 5.11 (m), 7.14-7.28 (m), 7.43 (d, J = 8.0 Hz), 7.64 (d, J = 8.8 Hz), 8.17 (d, J = 8.0 Hz), 8.43 (d, J = 7.0 Hz), 8.51 (s). MS calcd for $C_{46}H_{56}N_4O_5S$+Cs 909, found 909.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminal).

To cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) (0.57 g, 0.73 mmol) dissolved in 7 mL of DMSO was added o-iodoxybenzoic acid (0.61 g, 2.19 mmol). The reaction mixture was stirred at rt for 1.5 h. The DMSO was then removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and reconcentrated to remove any residual DMSO. Dilution with CH_2Cl_2 and reconcentration was repeated, and the residue was diluted with EtOAc to give a white precipitate which was filtered off. The solvent was washed with a 5% $Na_2S_2O_3$/5% $NaHCO_3$ solution, water, and brine before drying over $MgSO_4$. Removal of the solvent under vacuum gave 0.41 g (72%) of a white glassy solid which was used immediately without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.03 (m), 0.62 (m), 1.04-2.10 (m), 2.20-2.45 (m), 2.82 (s), 2.90 (m), 2.94 (s), 3.21 (m), 4.00 (m), 4.14 (m), 4.34 (m), 4.62 (m), 4.81 (m), 5.17 (m), 7.14-7.28 (m), 8.15 (d, J = 7.0 Hz), 8.25 (d, J = 7.0 Hz), 8.35 (d, J = 7.0 Hz), 8.41 (d, J = 7.0 Hz), 8.57 (s), 8.62 (s), 9.27 (s), 9.43 (s).

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Cyclopentylthiocarbonyl-L-Leu-N-Me-L-Phe-L-(Tr-glutaminal) (0.19 g, 0.25 mmol) was dissolved in 5 mL of THF. (Carbethoxymethylene)triphenylphosphorane (0.10 g, 0.30 mmol) was added, and the reaction was stirred overnight at rt. The solvent was removed in vacuo, and the residue purified by flash column chromatography on silica gel (gradient; 0-0.75 % $MeOH/CHCl_3$) to give 0.25 g of material that was contaminated by

triphenylphosphine oxide. This material was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.16 (m), 0.62 (m), 0.79 (d, J = 6.3 Hz), 1.10 (m), 1.20 (t, J = 7.0 Hz), 1.30-1.78 (m), 1.95 (m), 2.10-2.42 (m), 2.80 (s), 2.88 (m), 2.95 (s), 3.16 (m), 3.48 (m), 4.10 (q, J = 7.0 Hz), 4.11 (q, J = 7.0 Hz), 4.37 (m), 4.53 (m), 4.63 (m), 4.81 (m), 5.06 (m), 5.66 (d, J = 16.0 Hz), 5.93 (d, J = 16.0 Hz), 6.71 (dd, J = 16.0, 6.0 Hz), 6.80 (d, J = 16.0, 6.0 Hz), 7.13-7.28 (m), 7.97 (d, J = 8.0 Hz), 8.07 (d, J = 8.0 Hz), 8.16 (d, J = 7.0 Hz), 8.49 (d, J = 6.0 Hz), 8.55 (s), 8.60 (s).

Preparation of Product Ethyl-3-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.25 g) was dissolved in 5 mL of CH_2Cl_2. Trifluoroacetic acid (0.5 mL) was added, and the reaction was stirred at rt for 4 h. The solvent was removed in vacuo, and the residue purified by flash column chromatography on silica gel (gradient; 0-2 % MeOH/$CHCl_3$) to give 0.11 g (74% for two steps from the aldehyde intermediate) as a white amorphous solid: mp = 68-72 °C; IR(KBr) 3283, 2955, 1634, 1531, 1277, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.26 (m), 0.61 (m), 0.82 (d, J = 6.3 Hz), 0.83 (d, J = 6.3 Hz), 1.13 (m), 1.20 (t, J = 7.0 Hz), 1.30-2.12 (m), 2.77 (s), 2.90 (m), 2.94 (s), 3.11 (m), 3.47 (m), 4.10 (q, J = 7.0 Hz), 4.11 (q, J = 7.0 Hz), 4.38 (m), 4.50 (m), 4.67 (m), 4.81 (m), 5.04 (m), 5.69 (d, J = 15.0 Hz), 5.99 (d, J = 15.0 Hz), 6.72 (dd, J = 15.0, 5.5 Hz), 6.76 (bs), 6.83 (d, J = 15.0, 5.5 Hz), 7.12-7.30 (m), 7.99 (d, J = 8.0 Hz), 8.04 (d, J = 8.0 Hz), 8.19 (d, J = 8.0 Hz), 8.52 (d, J = 6.0 Hz). HRMS calcd for $C_{31}H_{46}N_4O_6S$+Cs 735.2192, found 735.2174. Anal. ($C_{31}H_{46}N_4O_6S$) C, H, N.

Example 5 - Preparation of Compound 6: 2-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, this intermediate was synthesized from cyclopentylthiocarbonyl-L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminal) (0.205 g, 0.264 mmol) and α-(triphenylphosphoranylidene)-γ-butyrolactone (0.12 g, 0.343 mmol) (prepared from α-bromo-γ-butyrolactone according to the procedure of J. E. Baldwin, et al., *Tetrahedron*; **1992**, *48*, 9373, the disclosure of which is entirely incorporated herein by reference) in 5 mL THF to give 0.28 g of product contaminated with triphenylphosphine oxide which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.12 (m), 0.60 (m), 0.79 (d, J=6.3 Hz), 1.10-2.18 (m), 2.10-2.49 (m), 2.80 (s), 2.89 (m), 2.94 (s), 3.09-3.57 (m), 4.30 (m), 4.42 (m), 4.85 (m), 5.01 (m), 6.26 (m), 6.42 (m), 7.10-7.29 (m), 8.01 (d, J= 8.0 Hz), 8.06 (d, J= 8.0 Hz), 8.18 (d, J= 7.0 Hz), 8.48 (d, J= 7.0 Hz), 8.53 (s), 8.59 (s).

Preparation of Product - 2-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γButyrolactone).

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, 2-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) was

synthesized from 2-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) in 49% yield (two steps from the aldehyde): white amorphous solid: mp = 87-91 °C: IR(KBr) 3286, 2963, 1749, 1668, 1634, 1531, 1452, 1205, 1138 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.12 (m), 0.58 (m), 0.83 (m), 1.08 (m), 1.20-1.79 (m), 2.01 (m), 2.77 (s), 2.84 (m), 2.94 (s), 3.12 (m), 3.53 (m), 4.26-4.43 (m), 4.68 (m), 4.96 (m), 6.26 (m), 6.39 (m), 6.76 (bs), 7.12-7.27 (m), 8.04 (m), 8.19 (d, J = 8.0 Hz), 8.50 (d, J = 7.0 Hz). HRMS calcd for $C_{31}H_{44}N_4O_6S$+Cs 733.2036, found 733.2053. Anal. ($C_{31}H_{44}N_4O_6S$ •0.75 $CHCl_3$) C, H, N.

Example 6 - Preparation of Compound 7: 1-(2',3'-Dihydroindolin-1-yl)-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.

Preparation of Intermediate BOC-L-Leu-L-N-Me-Phe-OMe.

N-Me-Phe-OMe•HCl (1.4 g) was dissolved in CH_2Cl_2 (50 mL) and poured into a combination of 1 N NaOH (aq, 7 mL) and sat. $NaHCO_3$ (25 mL). After mixing, the organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give the free amine as a clear colorless oil (1.14 g, 5.90 mmol). A solution of this amine and diisopropylethylamine (1.13 mL, 6.49 mmol) in DMF (10 mL) was added dropwise to a 0 °C solution of BOC-L-Leu (1.50 g, 6.49 mmol) and hydroxybenzotriazole hydrate (0.877 g, 6.49 mmol) in DMF (10 mL). Dicyclohexylcarbodiimide (1.47 g, 7.12 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, and was then stirred at rt for 48 h. The mixture was filtered to remove the precipitate, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with sat. $NaHCO_3$ (40 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography (25% EtOAc

in hexanes) to give BOC-L-Leu-L-N-Me-Phe-OMe as a white solid (2.04 g, 85%): mp = 126-127 °C; IR (thin film) 3401, 3319, 1743, 1708, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer) δ 0.92 (d, 3H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.5 Hz), 1.32-1.48 (m, 2H), 1.41 (s, 9H), 1.61-1.77 (m, 1H), 2.90 (s, 3H), 3.04 (dd, 1H, J = 14.5, 10.5 Hz), 3.37 (dd, 1H, J = 14.5, 5.5 Hz), 3.72 (s, 3H), 4.48-4.57 (m, 1H), 4.98-5.04 (m, 1H), 5.20 (dd, 1H, J = 10.5, 5.5 Hz), 7.16-7.32 (m 5H); Anal. ($C_{22}H_{34}N_2O_5$) C, H, N.

Preparation of Intermediate BOC-L-Leu-L-N-Me-Phe.

BOC-L-Leu-L-N-Me-Phe-OMe (0.625 g, 1.54 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C. A solution of 2 N NaOH (aq, 6.15 mL, 12.3 mmol) was added dropwise. The reaction mixture was stirred for 3 h at rt and poured into 10% aq $KHSO_4$ (150 mL). This mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated to give BOC-L-Leu-L-N-Me-Phe as a white foam (0.617 g, quantitative yield) which was used without purification.

Preparation of Intermediate [2-(2,3-Dihydroindol-1-yl)-2-oxo-ethyl]-Phosphonic Acid Diethyl Ester.

Oxalyl chloride (5.96 mL, 68.3 mmol) was added to a solution of diethylphosphonoacetic acid (12.8 g, 65.0 mmol) and DMF (0.03 mL, 0.39 mmol) in benzene (150 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 1 °h and then was concentrated under reduced pressure. The resulting oil was dissolved in THF (30 mL) and was added via cannula to a solution of indoline (7.38 g, 61.9 mmol) and triethylamine (10.9 mL, 78.0 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred at 0 °C

for 15 min, and then it was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a tan solid. Recrystallization from Et_2O provided [2-(2,3-dihydroindol-1-yl)-2-oxo-ethyl]-phosphonic acid diethyl ester (12.2 g, 63%) as a light brown solid: mp = 97-99 °C; IR (KBr) 3460, 1657, 1597, 1482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 6H, J = 7.2), 3.14 (d, 2H, J = 22.4), 3.22 (d, 2H, J = 8.4), 4.15-4.30 (m, 6H), 7.04 (t, 1H, J = 7.0), 7.17-7.28 (m, 2H), 8.21 (d, 1H, J = 9.0); Anal. ($C_{14}H_{20}NO_4P$) C, H, N.

Preparation of Intermediate 1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-Propenone.

Sodium bis(trimethylsilyl)amide (11.9 mL of a 1.0 M solution in THF, 11.9 mmol, 1.0 equiv) was added to a solution of [2-(2,3-dihydroindol-1-yl)-2-oxo-ethyl]-phosphonic acid diethyl ester (3.54 g, 11.9 mmol, 1.0 equiv) in THF (150 mL) at -78 °C, and the resulting solution was stirred for 20 min at that temperature. Crude BOC-L-(Tr-Glutaminal) (5.63 g, 11.9 mmol, 1 equiv) in THF (40 mL) was added via cannula, and the reaction mixture was stirred for 1 h at -78 °C, warmed to 0 °C for 10 min, and partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (50% EtOAc in hexanes) provided 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone as an off-white foam: IR (thin film) 3401, 3307, 1690, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.76-2.05 (m, 2H), 2.37-4.06 (m, 2H), 3.11-3.22 (m, 2H), 4.02-4.16 (m, 2H), 4.27-4.40 (m, 1H),

4.91-4.97 (m, 1H), 6.29 (d, 1H, J = 14.9), 6.77-6.96 (m, 2H), 6.98-7.05 (m, 1H), 7.14-7.37 (m, 17H), 8.25 (d, 1H, J = 7.5); Anal. ($C_{39}H_{41}N_3O_4$) C, H, N.

Preparation of Intermediate
1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe- L-(Tr-*Gln*)]-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.420 g, 0.682 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 3 mL) was added dropwise. After stirring for 2 h, the solvent was evaporated to give the amine salt which was used without purification. This crude amine salt was coupled to BOC-L-Leu-L-N-Me-Phe (0.302 g, 0.769 mmol) using the procedure described in Example 6 for the formation of BOC-L-Leu-L-N-Me-Phe-OMe to give 1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (after chromatography, 43% EtOAc in hexanes to 100% EtOAc) as an off-white foam (0.323 g, 53%): IR (thin film) 3401, 3295, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, J = 6.5 Hz), 0.85 (d, J = 6.8 Hz), 0.88 (d, J = 6.5 Hz), 1.04-1.21 (m), 1.23-1.48 (m), 1.34 (s), 1.41 (s), 1.56-1.67 (m), 1.82-1.94 (m), 1.95-2.09 (m), 2.26-2.36 (m), 2.90 (s), 2.99 (dd, J = 14.3, 10.4 Hz), 3.13-3.22 (m), 3.30 (dd, J = 14.3, 3.6 Hz), 3.97-4.18 (m), 4.38-4.47 (m), 4.55-4.77 (m), 4.83-4.90 (m), 6.18 (d, J = 14.0 Hz), 6.35-6.46 (m), 6.72 (s), 6.82-6.91 (m), 6.99-7.35 (m), 8.17 (d, J = 8.4 Hz), 8.25 (d, J = 8.1 Hz); Anal. ($C_{55}H_{63}N_5O_6$•0.75 H_2O) C, H, N.

Preparation of Intermediate 1-(2',3'-Dihydroindolin-1-yl)-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (0.315 g, 0.355 mmol) was dissolved in 1,4-dioxane (6 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 4 mL) was added dropwise. After stirring for 2 h, the solvent was evaporated to give the amine salt which was used without purification. This crude amine salt was dissolved in dry CH_2Cl_2 (8 mL) under argon, and diisopropylethylamine (0.136 mL, 0.781 mmol) was added. Ethyl chlorothiolformate (0.044 mL, 0.422 mmol) was added. The reaction solution was stirred 2 h and then poured into water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (50%-67% EtOAc in hexanes) to give 1-(2',3'-Dihydroindolin-1-yl)-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenone as a white foam (0.127 g, 41%): IR (thin film) 3284, 1660, 1637, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 0.59-0.76 (m), 0.82-0.89 (m), 1.15 (t, J = 7.3 Hz), 1.24 (t, J = 7.3 Hz). 1.32-1.44 (m), 1.52-1.76 (m), 1.83-2.11 (m), 2.04 (s), 2.25-2.36 (m), 2.63-3.41 (m), 2.88 (s), 2.89 (s), 3.94-4.19 (m), 4.34-4.44 (m), 4.50-4.72 (m), 5.82 (d, J = 7.5 Hz), 5.92 (d, J = 7.5 Hz), 6.22 (d, J = 14.6 Hz), 6.38 (d, J = 15.0 Hz), 6.65 (d, J = 8.4 Hz), 6.72-6.95 (m), 6.99-7.06 (m), 7.08-7.34 (m), 8.03 (d, J = 7.8 Hz), 8.22-8.28 (m); Anal. ($C_{53}H_{59}N_5O_5S$) C, H, N.

Preparation of Product 1-(2',3'-Dihydroindolin-1-yl)-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (0.110 g, 0.125 mmol) was deprotected using the procedure described in

Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give 1-(2',3'-dihydroindolin-1-yl)-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenone (after chromatography, 8% MeOH in CH_2Cl_2, and evaporation from Et_2O) as a white waxy material (0.044 g, 55%): IR (thin film) 3389, 3284, 3213, 1660, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.61-0.78 (m), 0.91 (d, J = 6.5 Hz), 0.92 (d, J = 6.2 Hz), 1.18-1.34 (m), 1.39-1.57 (m), 1.58-1.85 (m), 1.87-2.11 (m), 2.15-2.33 (m), 2.72-3.31 (m), 2.96 (s), 3.41-3.50 (m), 4.03-4.20 (m), 4.42-4.77 (m), 5.78 (d, J = 12.4 Hz), 6.01 (s, bs), 6.26-6.49 (m), 6.57 (d, J = 7.2 Hz), 6.80-6.97 (m), 6.99-7.35 (m), 7.91 (d, J = 8.1 Hz), 8.22-8.30 (m); Anal. ($C_{34}H_{45}N_5O_5S$) C, H, N.

Example 7 - Preparation of Compound 8: 2-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[BOC-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

BOC-L-(Tr-glutaminal) (290 mg, 0.614 mmol) and α-(triphenylphosphoranylidene)- γ-butyrolactone (255 mg, 0.737 mmol) (prepared from α-bromo-γ-butyrolactone according to the procedure of J. E. Baldwin, et al., *Tetrahedron*; **1992**, *48*, 9373, the disclosure of which is entirely incorporated herein by reference) were refluxed in DME (15 mL) / DMF (2 mL) for 2 h. Solvents were removed under vacuum, and the residue was purified by flash chromatography eluting with 50% EtOAc / hexane on silica gel to give 235 mg of 2-[BOC-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) as a white solid in 71% yield: IR (KBr) 3399, 3059, 2976, 2926, 1752, 1688, 1493, 1366, 1248, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.84 (m, 2 H), 2.38 (q, 2 H, J = 6.4 Hz) 2.80 (m, 1

H), 2.97 (m, 1 H), 4.22 (m, 1 H), 4.33 (t, 2 H, J = 7.2 Hz), 4.81 (m, 1 H), 6.43 (m, 1 H), 6.80 (s, 1 H), 7.19-7.32 (m, 15 H). Anal. ($C_{33}H_{36}N_2O_5{\cdot}H_2O$) C, H, N.

Preparation of Intermediate 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.577 g, 1.03 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 M, 3 mL) was added dropwise. The solution was stirred at rt for 2 h, at which time the solvent was evaporated to provide the amine HCl salt which was used without purification. The crude salt and BOC-L-Leu-L-N-Me-Phe (0.288 g, 1.03 mmol) were dissolved in dry CH_2Cl_2 (15 mL). Hydroxybenzotriazole-hydrate (0.209 g, 1.55 mmol), 4-methylmorpholine (0.34 mL, 3.09 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride (0.296 g, 1.55 mmol) were added successively. The reaction mixture was stirred at rt overnight and poured into water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.691 g, 82 %) as white foam: IR (thin film) 3301, 2958, 1753, 1675, 1494, 1173, 728 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 0.63-0.66 (m), 0.71-0.75 (m), 1.03-1.13 (m), 1.37 (s), 1.38 (s), 1.41 (s), 1.42 (s), 1.81-2.00 (m), 2.26-2.29 (m), 2.73-3.06 (m), 3.27 (d, J = 3.3 Hz), 3.32 (d, J = 3.3 Hz), 3.60-3.68 (m), 4.27-4.38 (m), 4.87 (d, J = 7.2 Hz), 6.50 (t, J = 3.3 Hz), 6.53 (t, J = 3.3 Hz), 6.70 (s), 7.09-7.13 (m), 7.19-7.34 (m), 7.44-7.50 (m), 7.64-7.71 (m), 8.21 (d, J = 3.6 Hz). Anal. ($C_{49}H_{58}N_4O_7{\cdot}0.45\ H_2O$) C, H, N.

Preparation of Intermediate 2-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.652 g, 0.8 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 M, 3 mL) was added dropwise. The solution was stirred at rt for 2 h, and the solvent was evaporated to provide the amine HCl salt which was used without purification. The crude amine HCl salt was dissolved in dry CH_2Cl_2 (10 mL), and Et_3N (0.335 mL, 2.4 mmol) was added. The reaction mixture was cooled to 0 °C, and ethyl chlorothiolformate (0.083 mL, 0.8 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h and then poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) as a white foam (0.389 g, 60%): IR (thin film) 3294, 2361, 1752, 1636, 1522, 1206 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$): δ 0.62-0.68 (m), 0.87 (d, 6.6 Hz), 1.19-1.29 (m), 1.37-1.42 (m), 1.89-1.94 (m), 2.28-2.31 (m), 2.71-3.12 (m), 3.65-3.78 (m), 4.31-4.34 (m), 4.55-4.58 (m), 5.66 (d, J = 6.3 Hz), 5.72 (d, J = 7.5 Hz), 6.40-6.43 (m), 6.51 (t, J = 3.0 Hz), 5.54 (t, J = 3.0 Hz), 6.75 (s), 7.09-7.12 (m), 7.21-7.34 (m), 7.44-7.50 (m), 7.53-7.58 (m), 7.64-7.71 (m), 8.06 (d, J = 7.5 Hz). Anal. ($C_{47}H_{54}N_4O_6S$) C, H, N.

Preparation of Product 2-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

2-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (202 mg, 0.25 mmol) was dissolved in 5 mL of dry CH_2Cl_2. Trifluoroacetic acid (4 mL) and triisopropylsilane (2 drops) were added sequentially to give a bright yellow solution. After stirring for 20 min, no yellow color remained. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) as a white solid (0.62 g, 42%): IR (thin film) 3239, 1638, 1526, 1209 cm^{-1}; ^1H NMR (mixture of rotamers) (DMSO-d_6) δ 0.57-0.65 (m), 0.82-0.85 (m), 1.11-1.17 (m), 1.35-1.50 (m), 1.68-1.80 (m), 1.98-2.06 (m), 2.71-2.97 (m), 3.10-3.17 (m), 4.26-4.46 (m), 4.69-4.71 (m), 5.00 (t, J = 7.5 Hz), 5.75 (s), 6.25-6.28 (m), 6.38-6.41 (m), 6.77 (s), 7.16-7.27 (m), 7.94 (d, J = 8.1 Hz), 8.03 (d, J = 7.5 Hz), 8.26 (d, J = 7.5 Hz), 8.54 (d, 6.9 Hz). Anal. ($C_{28}H_{40}N_4O_6S$•0.75 H_2O) C, H, N. HRMS calcd for $C_{28}H_{40}N_4O_6S$+Cs 693.1723, found 693.1739.

Example 8 - Preparation of Compound 9: Ethyl-3-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of cyclopentylthiocarbonyl- L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminol), CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) was synthesized from CBZ-L-hPhe and L-N-Me-Phe-L-(Tr-Glutaminol) in 71% yield: white amorphous solid: IR(KBr) 3295, 3061,

3027, 2936, 1659, 1495, 1447, 1261, 1043, 750, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.51 (m), 1.47 (m), 1.77 (m), 2.10-2.70 (m), 2.78 (s), 2.85 (s), 2.89 (m), 3.20 (m), 3.78 (m), 3.83 (m), 4.22 (m), 4.60-5.10 (m), 7.03-7.36 (m), 7.48 (m), 7.72 (d, J = 9.0 Hz), 7.84 (d, J = 7.0 Hz), 8.49 (s), 8.51 (s). Anal. ($C_{52}H_{54}N_4O_6$) C, H, N.

Preparation of Intermediate L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of L-N-Me-Phe-L-(Tr-glutaminol), L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) was synthesized from CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) in 96% yield: white amorphous solid: IR(KBr) 3331, 3057, 3029, 2936, 1657, 1493, 1449, 752, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (mixture of rotamers) 1.38-1.60 (m), 1.73 (m), 2.05-2.40 (m), 2.58 (m), 2.70 (s), 2.78 (s), 2.90 (m), 3.10-3.33 (m), 3.51 (m), 3.72 (m), 4.63 (m), 4.74 (m), 4.95 (m), 7.02-7.28 (m), 7.51 (d, J = 8.0 Hz), 8.50 (m), 8.55 (s). Anal. ($C_{44}H_{48}N_4O_4$) C, H, N.

Preparation of Intermediate Benzyl chlorothiolformate.

Using the procedure described in Example 4 for the preparation of cyclopentyl chlorothiolformate, benzyl chlorothiolformate was synthesized from benzylmercaptan in 71% yield: colorless liquid (bp 95-100 °C; 8 torr): IR(neat) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.19 (s, 2H), 7.30-7.34 (m, 5H). This compound is reported in the literature, for example, in J.J Willard et al., *J. Am. Chem. Soc.* **1960**, *82*, 4347, the disclosure of which is entirely incorporated herein by reference.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) (0.62 g, 0.88 mmol) was dissolved in 7 mL of CH_2Cl_2. Benzyl chlorothiolformate (0.134 mL, 0.88 mmol) dissolved in 2 mL of CH_2Cl_2 was added dropwise followed by 0.13 mL (0.90 mmol) of Et_3N. The reaction mixture was stirred for 15 minutes at rt, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (gradient: 0-1.5% MeOH/$CHCl_3$) to give 0.70 g (94%) of a white amorphous solid: IR(KBr) 3287, 3061, 3026, 2936, 1641, 1495, 1449, 1213, 750, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.56 (m), 1.30-1.90 (m), 2.10-2.44 (m), 2.79 (s), 2.84 (s), 2.95 (m), 3.15 (m), 3.83 (d, J = 13.6 Hz), 3.98 (d, J = 13.6 Hz), 4.04 (m), 4.41 (m), 4.57-4.70 (m), 4.82 (m), 5.07 (m), 7.02-7.29 (m), 7.48 (d, J = 8.0 Hz), 7.64 (d, J = 8.0 Hz), 8.47 (m), 8.52 (s), 8.76 (d, J = 7.0 Hz). Anal. ($C_{52}H_{54}N_4O_5S$•0.5 H_2O) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminal).

Using the procedure described in Example 4 for the preparation of cyclopentylthiocarbonyl- L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminal), benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminol) in 75% yield and used without further purification: white amorphous solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.60 (m), 2.20-2.49 (m), 2.81 (s), 2.84 (s), 2.95 (m), 3.24 (m), 3.80-4.05 (m), 4.17 (m), 4.42 (m), 4.59 (m), 4.95 (m), 5.24 (m), 7.03-7.29 (m), 8.29 (d, J = 9.0 Hz), 8.34 (d, J = 8.0 Hz), 8.47 (d, J = 8.0 Hz), 8.55 (s), 8.63 (s), 8.75 (d, J = 7.0 Hz), 9.26 (s), 9.39 (s).

Preparation of Intermediate
Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) to give material contaminated with triphenyphosphine oxide after chromatography which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.46 (m), 1.19 (t, J = 7.0 Hz), 1.63-1.91 (m), 2.26 (m), 2.44 (m), 2.80 (s), 2.82 (s), 2.94 (m), 3.17 (m), 3.82 (d, J = 14.0 Hz), 3.97 (d, J = 13.6 Hz), 4.09 (q, J = 7.0 Hz), 4.10 (q, J = 7.0 Hz), 4.45 (m), 4.98 (m), 5.12 (m), 5.67 (d, J = 14.0 Hz), 5.93 (d, J = 15.5 Hz), 6.71 (dd, J = 16.0, 5.5 Hz), 6.83 (dd, J = 15.5, 5.0 Hz), 7.02-7.29 (m), 8.05 (m), 8.44 (d, J = 8.0 Hz), 8.54 (s), 8.62 (s), 8.84 (d, J = 6.0 Hz).

Preparation of Product - Ethyl-3-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-3-(benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate in 81% yield as a white amorphous solid (two steps from the aldehyde intermediate): mp = 64-67°C: IR(KBr) 3285, 1641, 1537, 1454, 1208, 700 cm^{-1}, ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.42 (m), 1.19 (t, J = 7.0 Hz), 1.60-2.70 (m), 2.79 (s), 2.80 (s), 2.87 (m),

3.20 (m), 3.94-4.14 (m), 4.36-4.60 (m), 4.99 (m), 5.07 (m), 5.69 (d, J = 15.5 Hz), 5.99 (d, J = 15.5 Hz), 6.72 (dd, J = 15.5, 5.5 Hz), 6.76 (bs), 6.86 (dd, J = 15.5, 5.5 Hz), 6.98-7.30 (m), 8.03 (m), 8.50 (d, J = 8.0 Hz), 8.85 (d, J = 6.0 Hz). HRMS calcd for $C_{37}H_{44}N_4O_6S$+Cs 805.2036, found 805.2054. Anal. ($C_{37}H_{44}N_4O_6S$•0.45 $CHCl_3$) C, H, N.

Example 9 - Preparation of Compound 10: 2-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 5 for the preparation of 2-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone), 2-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) and (triphenylphosphoranylidene)-γ-butyrolactone to give material contaminated with triphenyphosphine oxide after column chromatography which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.63 (m), 1.39 (m), 1.62-1.90 (m), 2.80 (s), 2.82 (s), 2.10-2.95 (m), 3.10-3.28 (m), 3.85-4.05 (m), 4.24-4.40 (m), 4.45 (m), 4.62 (m), 4.82 (m), 5.07 (m), 6.26 (m), 6.39 (m), 7.02-7.30 (m), 8.05 (m), 8.49 (d, J = 8.0 Hz), 8.51 (s), 8.60 (s), 8.82 (d, J = 6.0 Hz).

Preparation of Product - 2-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 5 for the preparation of 2-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone),

2-(benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) was synthesized in 70% overall yield based on two steps from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe- L-(Tr-glutaminal): white amorphous solid (mp = 75-79 °C): IR(KBr) 3289, 1751, 1638, 1528, 1208, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.54 (m), 1.32 (m), 1.80 (m), 2.01-2.46 (m), 2.60 (m), 2.79 (s), 2.80 (s), 2.72-2.98 (m), 3.14 (m), 4.01 (d, J = 13.6 Hz), 4.05 (s), 4.12 (d, J = 13.6 Hz), 4.30-4.57 (m), 4.62 (m), 4.82 (m), 5.01 (m), 6.27 (m), 6.40 (m), 6.77 (m), 6.98-7.30 (m), 8.02 (d, J = 8.0 Hz), 8.08 (d, J = 9.0 Hz), 8.49 (d, J = 8.0 Hz), 8.83 (d, J = 6.0 Hz). HRMS calcd for $C_{37}H_{42}N_4O_6S$+Cs 803.1879, found 803.1863. Anal. ($C_{37}H_{42}N_4O_6S$•0.35 $CHCl_3$) C, H, N.

Example 10 - Preparation of Compound 11: Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This material was prepared from ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.397 g, 0.732 mmol) and BOC-L-Leu-L-N-Me-Phe (0.287 g, 0.731 mmol) as described in Example 6 for the formation of 1-(2',3'-dihydroindol-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (after chromatography, 44% EtOAc in hexanes) as a white foam (0.412 g, 69%): IR (thin film) 3295, 1713, 1672, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, J = 6.2 Hz), 0.66 (d, J = 6.5 Hz), 0.84 (d, J = 6.5 Hz), 0.88 (d, J = 6.5 Hz), 1.02-1.22 (m), 1.23-1.38 (m), 1.33 (s), 1.41 (s), 1.55-1.82 (m), 1.89-2.07 (m), 2.23-2.30 (m), 2.90 (s), 2.94 (s), 3.01 (dd, J = 14.6, 10.9 Hz), 3.03-3.13 (m), 3.26-3.37 (m), 3.27 (dd, J = 14.6, 3.4 Hz), 3.42-3.54 (m), 4.00-4.22 (m),

4.37-4.73 (m), 4.82-4.89 (m), 5.63-5.70 (m), 5.95 (dd, J = 15.9, 1.2 Hz), 6.23-6.28 (m), 6.66-6.75 (m), 6.79-6.89 (m), 7.09-7.34 (m), 8.14 (d, J = 8.7 Hz); Anal. ($C_{49}H_{60}N_4O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.390 g, 0.477 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.063 mL, 0.60 mmol) as described in Example 6 for the formation of 2,3-dihydroindole-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe- L-(Tr-*Gln*)]-E-propenamide to give ethyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate (after chromatography, 44% EtOAc in hexanes) as a white foam (0.261 g, 68%): IR (thin film) 3295, 1708, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.61-0.75 (m), 0.92 (d, J = 6.8 Hz), 0.68 (d, J = 6.5 Hz), 0.82-0.98 (m), 0.86 (d, J = 6.5 Hz), 0.87 (d, J = 6.2 Hz), 1.04-1.43 (m), 1.51-1.84 (m), 1.88-2.08 (m), 2.21-2.32 (m), 2.66-3.53 (m), 2.86 (s), 2.89 (s), 4.08-4.24 (m), 4.28-4.53 (m), 4.54-4.68 (m), 4.83-4.89 (m), 5.65-5.76 (m), 5.74 (d, J = 15.7 Hz), 5.96 (d, J = 15.7 Hz), 6.35-6.40 (m), 6.75 (dd, J = 15.7, 5.3 Hz), 6.80-6.89 (m), 7.09-7.35 (m), 8.03 (d, J = 7.5 Hz); Anal. ($C_{47}H_{56}N_4O_6S$) C, H, N.

Preparation of Product Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.220 g, 0.273 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give

ethyl-3-(ethylthiocarbonyl-L-Leu- L-N-Me-Phe-L-*Gln*)-E-propenoate (after chromatography, 50% acetone in hexanes) as a white foam (0.111 g, 72%): IR (thin film) 3284, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.62 (d, J = 6.5 Hz), 0.67 (d, J = 6.5 Hz), 0.89 (d, J = 6.5 Hz), 0.93 (d, J = 6.5 Hz), 1.22 (t, J = 7.2 Hz), 1.29 (t, J = 7.2 Hz), 1.37-2.04 (m), 2.13-2.44 (m), 2.58-3.36 (m), 2.93 (s), 3.12 (s), 4.17 (q, J = 7.2 Hz), 4.19 (q, J = 7.2 Hz), 4.37-4.90 (m), 4.96-5.15 (m) , 5.67 (d, J = 15.6 Hz), 6.00 (d, J = 15.6 Hz), 6.12 (s, bs), 6.62-6.72 (m), 6.87 (dd, J = 15.6, 5.9 Hz), 6.95 (bs), 7.12-7.35 (m), 7.47 (bs), 7.83 (d, J = 7.2 Hz); Anal. ($C_{28}H_{42}N_4S$•0.5 H_2O) C, H, N.

Example 11 - Preparation of Compound 12: 2-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)- E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate BOC-L-Val-L-N-Me-Phe-OMe.

N-Me-Phe-OMe·HCl (2.0 g) was dissolved in 50 mL of CH_2Cl_2 and poured into a combination of 1N NaOH (aq. 7 mL) and sat. $NaHCO_3$ (25 mL). After mixing, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the free base of the amine as a clear colorless oil (1.69 g, 8.75 mmol). A solution of this amine and diisopropylethylamine (1.68 mL, 9.62 mmol) in 10 mL of DMF was added dropwise to a solution of BOC-L-Val (2.09 g, 9.62 mmol) and hydroxybenzotriazole-hydrate (1.30 g, 9.62 mmol) in 10 mL DMF cooled to 0 °C. 1,3-Dicyclohexylcarbodiimide (2.18 g, 10.59 mmol) was then added. The reaction mixture was stirred at 0 °C for 1 h, and then stirred at rt. for 48 h. The mixture was filtered to remove the precipitate, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with sat. $NaHCO_3$

(100 mL), dried over Na_2SO_4, concentrated, and purified by flash column chromatography (15 % EtOAc in hexane) to give BOC-L-Val-L-N-Me-Phe-OMe as a white solid (2.56 g, 75 %). IR (thin film) 2972, 1743, 1710, 1646, 1497, 1172 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$): δ 0.34 (d, J = 6.9 Hz), 0.66 (d, J = 6.9 Hz), 0.89 (d, J = 6.9 Hz), 0.95 (d, J = 6.9 Hz), 1.41 (s), 1.87-1.98 (m), 2.92 (s), 2.94 (s), 2.99-3.01 (m), 3.37 (d, J = 5.7 Hz), 3.42 (d, J = 5.7 Hz), 3.72 (s), 3.73 (s), 4.35 (dd, J = 9.3, 6.0 Hz); 4.94-5.02 (m), 5.07 (d, J = 9.3 Hz), 5.34 (dd, J = 9.9, 3.0 Hz), 7.17-7.32 (m). Anal. ($C_{21}H_{32}N_2O_5$) C, H, N.

Preparation of Intermediate BOC-L-Val-L-N-Me-Phe.

BOC-L-Val-L-N-Me-Phe-OMe (0.396 g, 1.01 mmol) was dissolved in 10 mL of MeOH and cooled to 0 °C. A solution of 2 N NaOH (aq 4.04 mL, 8.08 mmol) was added dropwise. The reaction mixture was stirred for 2 h at rt. and poured into 10% aq $KHSO_4$ (80 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give BOC-L-Val-L-N-Me-Phe (0.38 g, quant.) which was used without purification.

Preparation of Intermediate 2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.546 g, 1.01 mmol) was deprotected and coupled with BOC-L-Val-L-N-Me-Phe (0.38 g, 1.01 mmol) using the procedure described in Example 7 for the formation of the 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) to give 2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) as a white foam

(0.613 g, 76%): IR (thin film) 3307, 2965, 1752, 1677, 1493, 1171 cm^{-1}; ^{1}H NMR (mixture of rotamers) ($CDCl_3$) δ 0.68 (d, J = 8.1 Hz), 0.81 (d, J = 6.6 Hz), 0.86 (d, J = 6.9 Hz), 1.38-1.45 (m), 1.78-2.00 (m), 2.25-2.27 (m), 2.64-2.99 (m), 3.28-3.47 (m), 3.55 (s), 3.59-3.76 (m), 4.04-4.07 (m), 4.24-4.31 (m), 4.42-4.46 (m), 4.74-4.80 (m), 4.90 (d, J = 6.9 Hz), 4.94-5.03 (m), 6.27-6.31 (m), 6.46-6.49 (m), 6.84 (s), 6.96 (s), 7.02 (s), 7.12-7.33 (m), 7.46-7.49 (m), 7.53-7.55 (m), 7.64-7.70 (m), 7.93 (d, J = 8.1 Hz); Anal. ($C_{48}H_{56}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Intermediate 2-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.376, 0.47 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.06 mL, 0.47 mmol) as described in Example 7 for the formation of 2-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) to give 2-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) as a white foam (0.150 mg, 40%): IR (thin film) 3299, 2965, 2360, 1751, 1493, 1205 cm^{-1}; ^{1}H NMR (mixture of rotamers) ($CDCl_3$) δ 0.36 (d, J = 6.9 Hz), 0.54 (d, J = 6.6 Hz), 0.71 (d, J = 6.9 Hz), 0.85 (d, J = 6.3 Hz), 1.21-1.31 (m), 1.82-1.84 (m), 2.28-2.30 (m), 2.64-3.03 (m), 3.31-3.41 (m), 3.62-3.78 (m), 4.24-4.33 (m), 4.45-4.52 (m), 4.60-4.66 (m), 5.81-5.89 (m), 6.33-6.36 (m), 6.41-6.49 (m), 6.86(s), 7.06 (s), 7.11-7.33 (m), 7.46-7.50 (m), 7.54-7.55 (m), 7.64-7.70 (m), 7.79 (d, J = 7.5 Hz). Anal. ($C_{46}H_{52}N_4O_6S$•0.5 H_2O) C, H, N.

Preparation of Product - 2-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

2-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) was deprotected using the procedure described in Example 7 for the formation of 2-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) to give 2-(ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) as a white solid (0.068 g, 96%): IR (thin film) 3748, 1625, 1541, 1200 cm^{-1}; ^{1}H NMR (mixture of rotamers) (DMSO-d_6) δ 0.27 (d, J = 6.6 Hz), 0.38 (d, J = 6.3 HZ), 0.55-0.59 (m), 0.79-0.84 (m), 1.11-1.17 (m), 1.70-1.83 (m), 1.88-1.95 (m), 1.98-2.07 (m), 2.72-3.26 (m), 4.05-4.10 (m), 4.25-4.44 (m), 4.64-4.66 (m), 5.12-5.18 (m), 5.33-5.36 (m), 6.23-6.26 (m), 6.34-6.39 (m), 6.75-6.78 (m), 7.12-7.26 (m), 7.78-7.84 (m), 8.13 (d, J = 7.5 Hz), 8.24-8.30 (m). HRMS calcd. for (M+Cs), 679.1566, found 679.1591. Anal. ($C_{27}H_{38}N_4O_6S{\cdot}0.3\ H_2O$) C,H,N.

<u>**Example 12 - Preparation of Compound 13: Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me- (4-Me-Phe)-L-*Gln*]-E-Propenoate**</u>

Preparation of Intermediate FMOC-L-N-Me-(4-Me)-Phe.

This N-protected amino acid was prepared in approximately 80% yield from FMOC-L-(4-Me)-Phe, purchased from Neosystem Laboratories, Strasbourg, France, using the procedure described by R.M. Friedinger, et al.; *J. Org. Chem.* **1983**, *48*, 77-81, the disclosure of which is entirely incorporated by reference herein. The crude product, isolated as an oil, was used without further purification: IR (thin film) 3452, 2953, 1713, 1516, 1451, 1404, 1321, 1194, 1040, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) mixture of rotamers; δ 2.27 (m), 2.77 (s), 2.79 (s), 2.85 (s), 3.08-3.32 (m), 3.37-3.49 (m), 4.10-4.26 (m), 4.30-4.45

(m), 4.80-4.89 (m), 5.05 (m), 6.87 (d, J = 11.0 Hz), 6.95 (d, J = 11.0 Hz), 7.09 (m), 7.25-7.55 (m), 7.75 (d, J = 7.4 Hz). MS calcd for $C_{26}H_{25}NO_4$+Na 438, found 438.

Preparation of Intermediate FMOC-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

FMOC-L-N-Me-(4-Me)-Phe (1.90 g, 4.6 mmol) was dissolved in 12 mL of CH_2Cl_2 and 2 mL of DMF. To this solution was added N-hydroxysuccinimide (0.53 g, 4.6 mmol) was added to this solution. Stirring was continued until all the solids were dissolved. N,N'-Dicyclohexylcarbodiimide (0.95 g, 4.6 mmol) was added to the reaction mixture, and the reaction was stirred at room temperature for two hours. The mixture was then filtered into a separate flask containing L-(Tr-Glutaminol) (1.72 g, 4.6 mmol) dissolved in 15 mL of DMF, removing the N,N'-dicyclohexylurea precipitate. The reaction mixture was stirred overnight at room temperature. The solvents were removed under vacuum, and the resulting crude product was purified by flash chromatography (5% saturated anhydrous NH_3 in MeOH/ CH_2Cl_2) on silica gel to give 3.72 g (90%) of a white solid: IR (KBr) 3407, 3312, 3059, 3032, 2932, 1665, 1516, 1491, 1447, 1319, 1188, 741, 700 cm^{-1}; ^1H NMR (DMSO-d_6) mixture of rotamers; δ 1.55 (m), 1.67 (m), 2.16 (bs), 2.23 (bs), 2.79 (s), 3.00-3.29 (m), 3.75 (m), 4.01-4.10 (m), 4.25 (m), 4.50-4.64 (m), 4.85 (m), 6.98-7.39 (m), 7.49 (d, J = 7.4 Hz), 7.60-7.75 (m), 7.87 (d, 1 H, J = 7.4 Hz), 8.50 (bs). MS calcd for $C_{50}H_{49}N_3O_5$+Na 794, found 794.

Preparation of Intermediate L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

FMOC-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) (3.32 g, 4.3 mmol) was dissolved in 11 mL of DMF. Piperidine (0.44 g, 5.2 mmol) was added dropwise to this solution. The

solution was stirred for 30 min. At this time, the solution was concentrated under vacuum, and the resulting crude amine was purified by flash chromatography (7% MeOH/ CH_2Cl_2) on silica gel to give 2.12 g (90%) of a white tacky foam: IR (thin film) 3302, 3057, 3025, 2934, 2865, 1956, 1925, 1809, 1659, 1516, 1265, 1035, 737, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (m, 1H), 1.89 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.37 (m, 2H), 2.67 (dd, 1H, J = 13.8, 9.0 Hz), 3.09 (dd, 1H, J = 13.4, 4.6 Hz), 3.20 (dd, 1H, J = 8.8, 4.4 Hz), 3.42 (m, 2H), 3.52 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H), 6.94 (m, 2H), 7.09 (m, 2H), 7.23-7.32 (m, 16H), 7.44 (d, 1 H, J = 7.7 Hz). MS calcd for $C_{35}H_{39}N_3O_3$+Cs 682, found 682.

Preparation of Intermediate CBZ-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Following the procedure of L. A. Carpino, *J. Am. Chem. Soc.* **1993,** *115*, 4397, the disclosure of which is entirely incorporated herein by reference, CBZ-L-hPhe was coupled with L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) as follows. To CBZ-L-hPhe (0.32 g, 1.0 mmol) was added 3 mL of DMF. To this solution was added L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) (0.55 g, 1.0 mmol) and diisopropylethylamine (0.26 g, 2.0 mmol). This solution was then cooled to 0 °C, and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.38 g, 1.0 mmol) was added. The solution instantly turned yellow, and the mixture was allowed to warm to rt. Once the starting materials were consumed as indicated by TLC, the reaction mixture was concentrated under vacuum. The residue was taken up in an excess of EtOAc (200 mL), and washed with 25 mL of H_2O, 25 mL 10% HCl twice, and then 5% aq $NaHCO_3$. The organic layer was dried over anh Na_2SO_4 and concentrated. The residue was subjected to flash chromatography (5% MeOH/ CH_2Cl_2) on silica gel to give 0.68 g (80%) of a white

solid: IR (KBr) 3403, 3059, 3030, 2947, 1662, 1516, 1448, 1264, 752, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 0.45 (m), 1.27-1.65 (m), 1.77-1.95 (m), 1.97 (s), 2.07-2.15 (m), 2.18 (s), 2.19-2.25 (m), 2.37 (m), 2.68-2.94 (m), 3.05-3.35 (m), 3.75 (m), 3.80 (m), 4.20-4.40 (m), 4.54-5.03 (m), 6.92-7.34 (m), 7.43-7.85 (m), 8.49 (m). MS calcd for $C_{53}H_{56}N_4O_6$+Cs 977, found 977.

Preparation of Intermediate L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Using the catalytic hydrogenation procedure described in Example 4 for the preparation of L-(Tr-Glutaminol), the amine was prepared in quantitative yield from CBZ-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol). White glassy solid: IR (KBr) 3378, 3057, 3027, 2938, 1659, 1516, 1493, 1447, 1180, 752, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 1.30-1.60 (m), 1.68 (m), 2.07 (m), 2.16 (s), 2.22 (m), 2.57 (m), 2.68 (s), 2.77 (s), 2.82-3.30 (m), 3.75 (m), 4.30-4.80 (m), 4.90-5.00 (m), 6.97-7.43 (m), 8.35-8.55 (m). MS calcd for $C_{45}H_{50}N_4O_4$+Na 733, found 733.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 8 for the preparation of benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol), benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminol) was prepared from L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminol) and benzyl chlorothiolformate in 96% yield. White solid: IR (KBr) 3418, 3316, 3054, 3023, 2947, 1678, 1666, 1643, 1530, 1493, 1451, 1211, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 0.55 (m), 1.25-1.60 (m),

1.80-1.93 (m), 1.96 (s), 2.19 (s), 2.22 (m), 2.40 (m), 2.68 (s), 2.72-2.96 (m), 3.17-3.27 (m), 3.40 (m), 3.65 (m), 3.80-4.10 (m), 4.54-5.03 (m), 6.84-7.29 (m), 7.47 (d, *J* = 8.1 Hz), 7.55 (d, *J* = 7.5 Hz), 7.66 (d, *J* = 8.4 Hz), 8.44-8.52 (m), 8.76 (d, *J* = 7.5 Hz). MS calcd for $C_{53}H_{56}N_4O_5S$+Na 883, found 883.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminal).

Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) was oxidized using o-iodoxybenzoic acid in anh. DMSO as described in Example 4 for the preparation of cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal). Upon workup, the aldehyde was used immediately without further purification. ^{1}H NMR ($CDCl_3$) mixture of rotamers; δ 0.89 (m), 1.26 (m), 1.67 (m), 1.85-2.05 (m), 2.13 (s), 2.22 (m), 2.28 (s), 2.35 (m), 2.60 (m), 2.70 (s), 2.83 (s), 2.89-2.95 (m), 2.99 (s), 3.01 (m), 3.25 (m), 3.90 (m), 4.04-4.25 (m), 4.30 (m), 4.61-4.66 (m), 5.85 (d, *J* = 7.0 Hz), 5.95 (d, *J* = 7.0 Hz), 6.22 (d, *J* = 7.0 Hz), 6.70-7.36 (m), 8.15 (d, *J* = 7.0 Hz). 9.35 (s), 9.40 (s).

Preparation of Intermediate Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe- L-(Tr-*Gln*)]-E-Propenoate.

This intermediate was prepared from benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminal) and (carbethoxymethylene)triphenylphosphorane as described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate. White solid: IR (thin film) 3297, 3057, 3027, 2980, 2928, 1714, 1651, 1516, 1495, 1447, 1267, 1213, 1035, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) mixture of rotamers; δ 0.88 (m), 1.26 (t, *J* = 7.2 Hz), 1.44 (m), 1.61-1.80

(m), 1.94 (m), 2.10 (s), 2.23 (m), 2.29 (s), 2.54 (m), 2.67 (s), 2.85 (s), 2.90 (m), 2.98 (s), 3.03 (m), 3.17-3.29 (m), 3.84-4.07 (m), 4.14 (m), 4.35 (m), 4.58 (m), 5.73 (dd, J = 15.8, 1.5 Hz), 5.91-5.99 (m), 6.04 (d, J = 7.7 Hz), 6.47 (d, J = 8.5 Hz), 6.72 (dd, J = 15.5, 5.1 Hz), 6.82 (m), 6.87-7.08 (m), 7.14-7.31 (m), 7.77 (d, J = 7.0 Hz). MS calcd for $C_{57}H_{60}N_4O_6S$+Na 951, found 951.

Preparation of Product - Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]- E-Propenoate.

This product was prepared in 69% overall yield (3 steps) from intermediate benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) by the deprotection of ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-propenoate using the procedure described in Example 4 for the synthesis of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate. White solid: IR (KBr) 3414, 3327, 3293, 3205, 3025, 2980, 2930, 1717, 1674, 1644, 1537, 1454, 1283, 1217, 1194, 700 cm^{-1}; ^1H NMR (DMSO-d_6) mixture of rotamers; δ 0.30 (m), 0.84 (m), 1.19 (t, J = 7.0 Hz), 1.33 (m), 1.77 (m), 1.92 (s), 2.05 (m), 2.20 (s), 2.40 (m), 2.57 (m), 2.77 (s), 2.80 (s), 2.84-2.90 (m), 3.05 (m), 3.94-4.14 (m), 4.36-4.60 (m), 5.01 (m), 5.63-5.73 (m), 6.01 (dd, J = 15.8, 1.1 Hz), 6.68-6.91 (m), 6.93-7.35 (m), 7.70 (m), 8.02 (m), 8.48 (d, J = 8.1 Hz), 8.65 (d, J = 8.0 Hz), 8.85 (d, J = 5.9 Hz). HRMS calcd for $C_{38}H_{46}N_4O_6S$+Cs 819.2192, found 819.2177. Anal. ($C_{38}H_{46}N_4O_6S$) C, H, N, S.

Example 13 - Preparation of Compound 14; Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This intermediate was prepared from benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminal) using (carbethoxyethylidene)triphenylphosphorane in place of (carbethoxymethylene)triphenylphosphorane in the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate. After column chromatography on silica gel (5% MeOH/CH_2Cl_2), two fractions were collected, one impure with triphenylphosphine oxide. (Analytical sample) White solid: IR (thin film) 3289, 3057, 3027, 2978, 2928, 1707, 1676, 1642, 1516, 1495, 1449, 1253, 1215, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) mixture of rotamers; δ 0.83 (m), 1.26 (m), 1.47-1.50 (m), 1.63-1.70 (m), 1.78 (m), 1.85 (d, J = 1.5 Hz), 1.87 (m), 1.92 (d, J = 1.5 Hz), 2.10 (s), 2.20 (m), 2.30 (s), 2.35-2.61 (m), 2.71 (s), 2.88 (s), 2.92 (m), 2.99 (s), 3.03-3.29 (m), 3.93 (d, J = 13.6 Hz), 4.06-4.23 (m), 4.35 (m), 4.52-4.69 (m), 5.94 (d, J = 7.4 Hz), 6.23 (d, J = 8.5 Hz), 6.28 (d, J = 7.7 Hz), 6.42 (dd, J = 9.0, 1.3 Hz), 6.58 (dd, J = 9.4, 1.3 Hz), 6.89 (bs), 6.92-7.17 (m), 7.20-7.33 (m), 7.64 (d, J = 7.7 Hz). MS calcd for $C_{58}H_{62}N_4O_6S$+Na 965, found 965.

Preparation of Product - Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]-E-Propenoate.

This product was prepared in 89% overall yield (3 steps) from intermediate benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) by the deprotection of ethyl-2-methyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-propenoa

te using the procedure described in Example 4 for the synthesis of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate. White solid: IR (KBr) 3302, 3223, 2984, 2928, 1709, 1672, 1642, 1535, 1453, 1256, 1217, 1132, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 0.34 (m), 1.17(m), 1.30 (m), 1.72 (m), 1.78 (s), 1.87 (s), 1.93 (s), 1.97-2.04 (m), 2.19 (s), 2.40 (m), 2.59 (m), 2.77 (s), 2.79 (s), 2.83 (m), 3.05 (m), 4.07 (m), 4.39 (m), 4.64 (m), 4.85 (m), 4.91 (m), 6.40 (d, J = 9.6 Hz), 6.54 (d, J = 8.5, 1.1 Hz), 6.74 (m), 6.76-7.30 (m), 7.99 (d, J = 8.1 Hz), 8.47 (d, J = 6.6 Hz), 8.84 (d, J = 6.3 Hz). HRMS calcd for $C_{39}H_{48}N_4O_6S$+Cs 833.2349, found 833.2329. Anal. ($C_{39}H_{48}N_4O_6S$) C, H, N, S.

Example 14 - Preparation of Compound 15: Ethyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me- Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-OMe.

To 2-isocyanato-4-methylvaleric acid methyl ester (0.86 g, 5.0 mmol) dissolved in 50 mL of THF was added benzyl mercaptan (0.59 mL, 5.0 mmol). The reaction mixture was stirred at rt overnight, and the solvent was removed in vacuo to give a yellow liquid which was purified by flash column chromatography on silica gel (gradient; 5-10% of EtOAc/hexanes) to give 1.39 g (94%) of benzylthiocarbonyl-L-Leu-OMe as a clear oil: IR (neat) 3320, 2957, 1746, 1651, 1520, 1454, 1200, 839, 702 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.97 (m, 6H), 1.65 (m, 3H), 3.74 (s, 3H), 4.16 (s, 2H), 4.60 (m, 1H), 5.72 (d, 1H, J = 8.0 Hz), 7.32 (m, 5H). Anal. ($C_{15}H_{21}NO_3S$) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu.

Benzylthiocarbonyl-L-Leu-OMe (0.85 g, 2.88 mmol) was dissolved in 30 mL of THF. To this solution was added 1N LiOH (3.0 mL, 3.0 mmol), and the reaction mixture was stirred at rt overnight. At this time an additional 1.5 mL of 1N LiOH was added, and the reaction mixture was further stirred for 4 h. At this time, an additional 1.5 mL of 1N LiOH was added. After another 3 h at room temperature, the pH was adjusted to 7 with 10% HCl, and the THF was removed in vacuo. The aqueous phase was washed with Et_2O and separated, then adjusted to pH 1-2. The product was extracted with CH_2Cl_2, and the organic phase washed with brine, dried over $MgSO_4$, filtered, and then concentrated to give 0.29 g of benzylthiocarbonyl-L-Leu as a clear liquid that was contaminated with benzyl mercaptan: ^{1}H NMR (DMSO-d_6) δ 0.83 (d, 3H, J = 6.0 Hz), 0.87 (d, 3H, J = 6.0 Hz), 1.45 (m, 3H), 4.04 (s, 2H), 4.22 (m, 1H), 7.27 (m, 5H), 8.46 (d, 1H, J = 7.0 Hz). MS calcd for $C_{14}H_{19}NO_3S$+H 282, found 282.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of cyclopenylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol), benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) was synthesized from L-N-Me-Phe-L-(Tr-glutaminol) and benzylthiocarbonyl-L-Leu in 58% yield: white amorphous solid: IR(KBr) 3289, 3057, 3027, 2953, 1638, 1493, 1449, 1206, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.19 (m), 0.60 (m), 0.79 (d, J = 6.2 Hz), 0.80 (d, J = 6.2 Hz), 1.12-1.77 (m), 2.12-2.36 (m), 2.84 (s), 2.90 (m), 2.96 (s), 3.12-3.40 (m), 3.63

(m), 3.84 (d, J = 13.6 Hz), 3.96 (d, J = 13.6 Hz), 4.02 (s), 4.33 (m), 4.66 (m), 5.06 (m), 7.10-7.28 (m), 7.47 (d, J = 9 Hz), 7.61 (d, J = 8.5 Hz), 8.35 (d, J = 7.0 Hz), 8.51 (s), 8.56 (d, J = 7.0 Hz). Anal. ($C_{48}H_{54}N_4O_5S$) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminal).

Using the procedure described in Example 4 for the preparation of cyclopenylthiocarbonyl- L-Leu-L-N-Me-Phe-L-(Tr-glutaminal), benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) in 93% yield and was used without further purification: white amorphous solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.02 (m), 0.61 (d, J = 6.6 Hz), 0.64 (d, J = 6.6 Hz), 0.81 (d, J = 6.2 Hz), 1.05-1.75 (m), 1.98 (m), 2.23-2.48 (m), 2.84 (s), 2.93 (m), 2.96 (s), 3.23 (m), 3.84 (d, J = 13.6 Hz), 3.95 (d, J = 14.0 Hz), 4.01 (m), 4.12 (m), 4.42 (m), 4.71 (m), 4.83 (m), 5.18 (m), 7.11-7.28 (m), 8.27 (d, J = 8.0 Hz), 8.31 (m), 8.57 (m), 8.62 (s), 9.27 (s), 9.40 (s).

Preparation of Intermediate Ethyl-3-[Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-Tr-*Gln*)]- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) to give 0.30 g of material contaminated with triphenylphosphine oxide after chromatography which was used without further purification: white amorphous solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ

-0.12 (m), 0.86 (d, J = 6.2 Hz), 0.87 (d, J = 6.2 Hz), 1.23 (t, J = 7.0 Hz), 1.26 (t, J = 7.0 Hz), 1.49 (m), 1.72 (m), 2.10-2.45 (m), 2.88 (s), 2.96 (m), 3.03 (s), 3.17 (m), 3.83 (d, J = 13.6 Hz), 3.96 (d, J = 13.6 Hz), 4.03 (s), 4.08 (m), 4.39 (m), 4.50 (m), 4.66 (m), 4.81 (m), 5.08 (m), 5.72 (d, J = 16.0 Hz), 6.01 (d, J = 15.8 Hz), 6.77 (dd, J = 15.6, 6.0 Hz), 6.89 (dd, J = 15.8, 6.0 Hz), 7.16-7.34 (m), 8.09 (d, J = 8.0 Hz), 8.43 (d, J = 8.0 Hz), 8.63 (s), 8.68 (s), 8.70 (d, J = 7.0 Hz).

Preparation of Product Ethyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)-E-propenoate in 41% yield (two steps from the aldehyde intermediate): white amorphous solid: mp = 60-63 °C): IR(KBr) 3289, 2957, 1638, 1533, 1453, 1277, 1209, 700 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.26 (m), 0.60 (m), 0.83 (d, J = 6.2 Hz), 1.17 (t, J = 7.0 Hz), 1.20 (t, J = 7.0 Hz), 1.03-1.60 (m), 1.66-1.98 (m), 2.01 (m), 2.80 (s), 2.92 (m), 2.96 (s), 3.25 (m), 3.92-4.18 (m), 4.38 (m), 4.48 (m), 4.68 (m), 4.86 (m), 5.08 (m), 5.69 (d, J = 16.0 Hz), 5.99 (d, J = 16.0 Hz), 6.69-6.76 (m), 6.86 (dd, J = 16.0, 6.0 Hz), 7.14-7.29 (m), 8.00 (m), 8.36 (d, J = 8.5 Hz), 8.64 (d, J = 6.6 Hz). HRMS calcd for $C_{33}H_{44}N_4O_6S$+Cs 757.2036, found 757.2008. Anal. ($C_{33}H_{44}N_4O_6S$) C, H, N.

Example 15 - Preparation of Compound 16: Ethyl-2-Methyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate
Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-Leu-L-N-Me-Phe- L-(Tr-*Gln*)]-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-2-methyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) (0.2 g, 0.25 mmol) and (carbethoxyethylidene) triphenylphosphorane (0.11 g, 0.3 mmol) in 5 mL THF to give 0.12 g of material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient; 0-1% MeOH/$CHCl_3$) which was used without further purification. White amorphous solid: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -.012 (m), 0.61 (m), 0.80 (d, J = 6.2 Hz), 1.10-1.34 (m), 1.38-1.74 (m), 1.76 (s), 1.81 (s), 2.10-2.48 (m), 2.83 (s), 2.94 (s), 3.13 (m), 3.85 (d, J = 14.0 Hz), 3.98 (d, J = 14.0 Hz), 4.02 (s), 4.09 (m), 4.35 (m), 4.57 (m), 4.73 (m), 4.97 (m), 6.38 (d, J = 10.0 Hz), 6.53 (d, J = 9.0 Hz), 7.10-7.28 (m), 7.98 (m), 8.35 (d, J = 8.0 Hz), 8.51 (s), 8.58 (s), 8.63 (d, J = 6.0 Hz).

Preparation of Product
Ethyl-2-Methyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-2-methyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-2-methyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate in 24% yield (two steps from the aldehyde intermediate). White amorphous

solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.16 (m), 0.59 (m), 0.84 (m), 1.08-1.83 (m), 1.78 (s), 1.86 (s), 2.03 (m), 2.79 (s), 2.94 (s), 3.16 (m), 3.97-4.21 (m), 4.35 (m), 4.53-4.78 (m), 5.08 (m), 6.39 (d, J = 9.0 Hz), 6.55 (d, J = 9.0 Hz), 6.82 (m), 7.12-7.29 (m), 7.96 (m), 8.35 (d, J = 6.6 Hz), 8.65 (d, J = 7.0 Hz). HRMS calcd for $C_{34}H_{46}N_4O_6S$+Cs 771.2192, found 771.2172. Anal. ($C_{34}H_{46}N_4O_6S$) C, H, N.

<u>Example 16 - Preparation of Compound 17: 1-[2'-Oxazolidon-3'-yl]-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.</u>

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-Propenone.

To 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (1.0 g, 1.94 mmol) in 12.0 mL of anh THF was added triethylamine (0.68 mL, 4.86 mmol). The mixture was cooled to -20 °C and pivaloyl chloride (0.24 mL, 1.94 mmol) was added. The reaction mixture was stirred at -20 °C for 2.5 h, at which time solid lithium chloride (0.091 g, 2.14 mmol) and 2-oxazolidone (0.17 g, 1.94 mmol) were added. The reaction mixture was allowed to warm to rt and further stirred overnight. The mixture was then concentrated to dryness, and the residue was taken up in CH_2Cl_2 and washed with 5% $KHSO_4$. The organic layer was separated, and the aqueous layer was reextracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to yield 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.61 g, 54 %) as an off-white solid foam. ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 4.5 H), 1.43 (s, 4.5 H), 1.81 (m, 1H), 1.98 (m, 1H), 2.40 (t, 2H, J = 7.2 Hz), 4.02-4.08 (m, 2H), 4.37-4.44 (m, 3H), 4.88 (d, 1H, J = 8.1 Hz),

6.87 (bs, 1H), 6.99 (dd, 1H, J = 15.8, 5.2 Hz), 7.18-7.32 (m, 16H). MS calcd for $C_{34}H_{37}N_3O_6$+H 584, found 584.

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]- E-Propenone.

To 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.60 g, 1.02 mmol) dissolved in isopropyl alcohol (17.25 mL), $HClO_4$ (5.0 mL, 79.63 mmol) was added, and the reaction mixture was stirred at rt for 1.5 h. The mixture was then poured into an aq solution of 1N NaOH (3.0 mL) along with a sat. $NaHCO_3$ solution (30.0 mL) and was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated to give the free amine (0.46 g, 0.96 mmol), which was coupled immediately with BOC-L-Leu-L-N-Me-Phe (0.38 g, 0.96 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate to provide 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]- E-propenone (0.33 g, 41 %) as a tan solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.65 (t, J = 6.8 Hz), 0.72 (m), 0.84-0.89 (m), 1.07 (m), 1.24-1.44 (m), 1.63 (m), 1.84 (m), 2.08 (m), 2.28-2.36 (m), 2.90 (s), 3.01 (m), 3.34 (m, 4.01-4.06 (m), 4.16 (m), 4.38-4.42 (m), 4.64 (m), 4.73 (m), 4.85 (m), 6.76 (bs), 7.04 (dd, J = 15.5, 6.1 Hz), 7.12-7.41 (m), 8.29 (d, J = 8.4 Hz). MS calcd for $C_{50}H_{59}N_5O_8$+H 858, found 858.

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-Propenone.

1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-propenone (0.32 g, 0.37 mmol) was deprotected with $HClO_4$ using the procedure described in the previous

preparation and was subsequently coupled to ethylchlorothiolformate (0.042 mL, 0.40 mmol) using the procedure described in Example 6 for the preparation of 2,3-dihydroindole-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide to provide 1-[2'-oxazolidon-3'-yl]-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-propenone (0.22 g, 78 %) as an off-white solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.62-0.76 (m), 0.85-0.87 (m), 1.13-1.26 (m), 1.37 (m), 1.62 (m), 1.85 (m), 2.06 (m), 2.58-2.72 (m), 2.67-2.89 (m), 3.18-3.40 (m), 4.02-4.07 (m), 4.39-4.44 (m), 4.64-4.67 (m), 5.71 (m), 6.76 (bs), 7.00 (m), 7.14-7.35 (m), 8.06 (d, J = 8.4 Hz). MS calcd for $C_{48}H_{55}N_5O_7S$+Cs 978, found 978.

Preparation of Product - 1-[2'-Oxazolidon-3'-yl]-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-Propenone.

1-[2'-Oxazolidon-3'-yl]-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-propenone (0.22 g, 0.26 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide 1-[2'-oxazolidon-3'-yl]-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-propenone (0.056 g, 35 %) as a white solid: mp = 110-111 °C; IR (thin film) 3272, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.64-0.70 (m), 0.89-0.91 (m), 1.19-1.28 (m), 1.40 (m), 1.65 (m), 2.03 (m), 2.23-2.25 (m), 2.76-2.96 (m), 3.48 (q, J = 7.2 Hz), 4.04-4.10 (m), 4.41-4.46 (m), 4.65-4.67 (m), 5.48 (m), 6.12 (m), 6.24 (bs), 7.02 (m), 7.15-7.36 (m), 7.91 (m). HRMS calcd for $C_{29}H_{41}N_5O_7S$+Cs 736.1780, found 736.1803; Anal ($C_{29}H_{41}N_5O_7S$) C, H, N.

Example 17 - Preparation of Compound 18:
Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]- E-Propenoate.

Preparation of Intermediate BOC-L-(3R-Phenyl)-Pro.

(2S, 3R)-3-Phenylpyrrolidine-2-carboxylic acid (0.10 g, 0.52 mmol) was suspended in 1,4-dioxane and 800 mL of 1N NaOH was added to form a clear solution. Di-*tert*-butyl dicarbonate (0.13 g, 0.58 mmol) was added over a period of 30 minutes, and the reaction mixture was stirred overnight at rt. At this time, the reaction mixture was concentrated in vacuo, and the resulting residue was taken up in a saturated solution of $NaHCO_3$. This solution was washed with ether, and the aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic phase was separated and dried over $MgSO_4$ and concentrated to provide BOC-L-(3R-phenyl)-Pro (0.15 g, 97%) as a white solid. ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.03 (m, 1H), 2.35 (m, 1H), 3.49-3.83 (m, 4H), 7.33-7.35 (m, 5H). MS calcd for $C_{16}H_{21}NO_4$+H 292, found 292.

Preparation of Intermediate
Ethyl-3-[BOC-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.28 g, 0.52 mmol) was deprotected and coupled to BOC-L-(3R-phenyl)-Pro using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 73%) as a white glassy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25-1.31 (m, 3H), 1.40 (bs, 9H), 2.03 (m, 2H), 2.41 (m, 2H), 3.48 (m, 2H), 3.67 (m, 2H), 4.14-4.21 (m, 4H), 4.68 (m, 1H), 5.62 (d, 1H, J = 16.5 Hz), 6.32 (m, 1H), 6.75 (dd, 1H, J =

15.9, 5.0 Hz), 6.96 (s, bs, 1H), 7.20 - 7.33 (m, 20H). MS calcd for $C_{44}H_{49}N_3O_6$+H 716, found 716.

Preparation of Intermediate - Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate was deprotected and coupled to CBZ-Leu (0.10 g, 0.37 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.19 g, 60%) as a white glassy solid. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz), 1.94 (m, 1H), 1.29 (t, 3H, J = 7.2 Hz), 1.34 - 1.51 (m, 2H), 2.07 (m, 1H), 2.23 (m, 1H), 2.37 (m, 1H), 2.44 - 2.48 (m, 2H), 3.50-3.52 (m, 2H), 3.67-3.69 (m, 2H), 4.04 - 4.19 (m, 4H), 4.45-4.52 (m, 2H), 4.80 (d, 1H, J = 9.0 Hz), 5.05 (d, 1H, J = 12.1 Hz), 5.12 (d, 1H, J = 12.1 Hz), 5.44 (dd, 1H, J = 15.6, 1.9 Hz), 5.65 (d, 1H, J = 8.7 Hz), 6.66 (dd, 1H, J = 15.7, 4.5 Hz), 7.17-7.38 (m, 25H); MS calcd for $C_{53}H_{58}N_4O_7$+H 863, found 863.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)- E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-*Gln*]-E-propenoate (0.098 g, 70%) as a white solid after column chromatography on silica (5% methanol/$CHCl_3$). mp = 72-75 °C; IR (thin film) 3311, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H, J = 7.2 Hz), 1.30 (t, 3H, J =

7.0 Hz), 1.44-1.57 (m, 4H), 1.75 (m, 1H), 2.10 (m, 1H), 2.17-2.28 (m, 2H), 2.34-2.43 (m, 2H), 3.51 (m, 1H), 3.73 (m, 1H), 4.13-4.20 (m, 3H), 4.59-4.66 (m, 2H), 5.11 (bs, 2H), 5.25 (bs, 1H), 5.37-5.47 (m, 2H), 5.71 (d, 1H, *J* = 9.0 Hz), 6.57 (bs, 1H), 6.70 (dd, 1H, *J* = 15.7, 4.5 Hz), 7.25-7.41 (m, 10H). HRMS calcd for $C_{34}H_{44}N_4O_7$+Cs 753.2264, found 753.2240. Anal ($C_{34}H_{44}N_4O_7$) C, H, N.

<u>Example 18 - Preparation of Compound 19: Ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.</u>

Preparation of Intermediate Ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 0.55 mmol) was deprotected and coupled to BOC-L-Pro (0.11 g, 0.55 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 85%) as a white glassy solid after column chromatography on silica (5% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.2 Hz), 1.43 (bs, 10H), 1.82-2.00 (m, 6H), 2.34 (t, 2H, *J* = 7.2 Hz), 3.34 (m, 2H), 4.14-4.21 (m, 3H), 4.62 (m, 1H), 5.92 (dd, 1H, *J* = 15.6, 1.5 Hz), 6.80 (dd, 1H, *J* = 15.7, 5.1 Hz), 7.18-7.33 (m, 16H). MS calcd for $C_{38}H_{45}N_3O_6$+Cs 772, found 772.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 0.47 mmol) was deprotected and coupled with CBZ-Leu (0.12 g, 0.47 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 64%) as a white

foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.92 (d, 3H, J = 6.2 Hz), 1.27 (t, 3H, J = 7.0 Hz) 1.35 (m, 1H), 1.63-1.75 (m, 2H), 1.99-2.10 (m, 5H), 2.39 (m, 2H), 3.53 (m, 1H), 3.73-3.76 (m, 3H), 4.17 (q, 2H, J = 7.2 Hz), 4.26 (m, 1H), 4.49-4.51 (m, 3H), 5.02-5.12 (m, 3H), 5.85 (dd, 1H, J = 15.9, 1.6 Hz), 6.78 (dd, 1H, J = 15.7, 5.1 Hz), 7.07 (bs, 1H), 7.19-7.33 (m, 20H). MS calcd for $C_{47}H_{54}N_4O_7$+Cs 919, found 919.

Preparation of Product - Ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.22 g, 0.28 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe- L-*Gln*)-E-propenoate, to provide ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-propenoate (0.092 g, 61%) as a white solid after preparative TLC (10% methanol/$CHCl_3$): mp = 55-60 °C; IR (thin film) 3300, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.5 Hz), 0.98 (d, 3H, J = 6.5 Hz) 1.28 (t, 3H, J = 7.2 Hz), 1.46 (t, 2H, J = 7.0 Hz), 1.70-1.75 (m, 2H), 2.03-2.33 (m, 7H), 3.60 (m, 1H), 3.79 (m, 1H), 4.19 (q, 2H, J = 7.2 Hz), 4.41 (m, 1H), 4.54-4.65 (m, 2H), 5.08 (dd, 2H, J = 15.4, 12.3 Hz), 5.54 (m, 1H), 5.44 (d, 1H, J = 8.4 Hz), 5.91 (dd, 1H, J = 15.7, 1.4 Hz), 6.36 (m, 1H), 6.77 (d, 1H, J = 8.7 Hz), 6.84 (dd, 1H, J = 15.9, 5.0 Hz), 7.34 (bs, 5H). HRMS calcd for $C_{28}H_{40}N_4O_7$+Cs 677.1951, found 677.1972. Anal ($C_{28}H_{40}N_4O_7$•$0.5H_2O$) C, H, N.

Example 19 - Preparation of Compound 20: Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-(4R-Benzyloxy)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.50 g, 0.92 mmol) was deprotected and coupled to BOC-L-(4R-benzyloxy)-Pro (0.30 g, 0.92 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[BOC-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.54 g, 78%) as a white foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.16 Hz), 1.39 (bs, 10H), 1.80 (m, 1H), 1.80 (m, 1H), 2.16 (m, 1H), 2.32 - 2.39 (m, 2H), 3.46-3.51 (m, 2H), 4.18 (q, 2H, J = 7.2 Hz), 4.26-4.35 (m, 2H), 4.46-4.49 (m, 2H), 4.56-4.66 (m, 2H), 5.90 (dd, 1H, J = 15.7 Hz), 6.80 (dd, 1H, J = 15.6, 4.8 Hz), 6.97 (m, 1H), 7.18-7.37 (m, 20H). MS calcd for $C_{45}H_{51}N_3O_7$+H 746, found 746.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.49 g, 0.72 mmol) was deprotected and coupled to CBZ-Leu (0.19 g, 0.72 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.47 g, 72%) as a white foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 6.5 Hz), 1.29-1.35 (m, 4H), 1.75 (m,

1H), 2.45 (m, 1H), 2.19-2.23 (m, 2H), 2.40-2.46 (m, 2H), 3.60 (m, 1H), 3.87 (m, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.27-4.37 (m, 2H), 4.48-4.54 (m, 5H), 4.97-5.09 (m, 4H), 5.83 (dd, 1H, J = 15.7, 1.7 Hz), 6.673 (d, 1H, J = 7.5 Hz), 6.78 (dd, 1H, J = 15.7, 5.1 Hz), 7.09 (bs, 1H), 7.15-7.36 (m, 25H). MS calcd for $C_{54}H_{60}N_4O_8$+H 893, observed 893.

Preparation of Product -
Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.47 g, 0.52 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-*Gln*]-E-propenoate (0.27 g, 81%) as a white foamy solid after column chromatography on silica (5% methanol/$CHCl_3$). IR (thin film) 3296, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90- 0.96 (m, 6H), 1.28 (t, 3H, J = 7.0 Hz), 1.44-1.46 (m, 2H), 1.69-1.71 (m, 2H), 2.07-2.37 (m, 5H), 3.67 (dd, 1H, J = 10.7, 4.5 Hz), 4.03 (d, 1H, J = 10.9 Hz), 4.16 (d, 1H, J = 7.2 Hz), 4.21 (d, 1H, J = 7.2 Hz), 4.32 (m, 1H), 4.46-4.55 (m, 4H), 4.62 (m, 1H), 5.02 (d, 1H, J = 12.3 Hz), 5.09 (d, 1H, J = 12.3 Hz), 5.31 (m, 1H), 5.46 (d, 1H, J = 9.0 Hz), 5.89 (dd, 1H, J = 15.9, 1.6 Hz), 6.43 (m, 1H), 6.65 (d, 1H, J = 9.0 Hz), 6.83 (dd, 1H, J = 15.7, 5.1 Hz), 7.33 (bs, 10H). HRMS calcd for $C_{35}H_{46}N_4O_8$+Cs 783.2370, found 783.2390; Anal ($C_{35}H_{46}N_4O_8$•0.5 H_2O) C, H, N.

Example 20 - Preparation of Compound 21:
Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-*Gln*]- E-Propenoate.

Preparation of Intermediate BOC-L-(3S-Methyl)-Pro.

(2S, 3S)-3-Methyl pyrrolidine-2-carboxylic acid (0.25 g, 1.94 mmol) was protected with a BOC group following the procedure described in Example 17 for the preparation of BOC-L-(3R-Phenyl)-Pro to provide BOC-L-(3S-methyl)-Pro (0.43 g, 98%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.16-1.21 (m, 6H), 1.42 (s, 9H), 1.48 (s, 9H), 1.52-1.61 (m, 2H), 2.01-2.12 (m, 2H), 2.41 (m, 1H), 2.61 (m, 1H), 3.41-3.62 (m, 4H), 3.77 (m, 1H), 3.90 (m, 1H). MS calcd for $C_{11}H_{19}NO_4$+H, 230, found 230.

Preparation of Intermediate Ethyl-3-[BOC-L-(3S-Methyl)-Pro-L-(Tr-*Gln*)] -E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.53 g, 0.97 mmol) was deprotected and coupled to BOC-L-(3S-methyl)-Pro (0.22 g, 0.97 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 43%) as a glassy off-white solid foam after column chromatography on silica (5% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.10-1.17 (m, 3H), 1.27 (t, 3H, J = 7.2 Hz), 1.41 (bs, 10H), 1.58 (bs, 2H), 1.80 (m, 1H), 2.00 (m, 1H), 2.36 (m, 2H), 3.30 (m, 1H), 3.40-3.66 (m, 2H), 3.70 (d, 1H, J = 5.0 Hz), 4.14-4.21 (m, 2H), 4.64 (m, 1H), 5.92 (d, 1H, J = 15.9 Hz), 6.78-6.84 (m, 2H), 7.19-7.29 (m, 15H). MS calcd for $C_{39}H_{47}N_3O_6$+H, 654, found 654.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 0.42 mmol) was deprotected and coupled to CBZ-Leu (0.11 g, 0.42 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 52%) as a white solid foam after column chromatography on silica (4% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.2 Hz), 0.92 (d, 3H, J = 6.2 Hz), 1.10 (d, 3H, J = 7.2 Hz), 1.34 (m, 1H), 1.60-1.74 (m, 2H), 2.04-2.17 (m, 3H), 2.38-2.48 (m, 3H), 3.53 (m, 1H), 3.68 (d, 1H, J = 6.2 Hz), 3.91 (m, 1H), 4.17 (dd, 2H, J = 14.9, 6.8 Hz), 4.48-4.52 (m, 2H), 4.96-5.12 (m, 4H), 5.84 (d, 1H, J = 15.6 Hz), 6.49 (d, 1H, J = 8.1 Hz), 6.79 (dd, 1H, J = 16.2, 4.7 Hz), 7.13 (bs, 1H), 7.19-7.33 (m, 20H). MS calcd for $C_{48}H_{56}N_4O_7$+H, 801, found 801.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 0.22 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-*Gln*]-E-propenoate (0.078 g, 64%) as a white solid foam after column chromatography on silica (4% methanol/$CHCl_3$). IR (thin film) 3392, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92–0.98 (m, 6H), 1.17 (d, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.41–1.49 (m, 2H), 1.64–1.76 (m, 3H), 2.10–2.28 (m, 3H), 2.35–2.48 (m, 2H), 3.59 (m, 1H), 3.85 (d, 1H, J = 6.5 Hz), 3.96 (m, 1H), 4.19 (dd, 1H, J = 14.3, 7.2 Hz), 4.54 (m, 1H), 4.68 (m, 1H),

5.04–5.13 (m, 2H), 5.31 (d, 1H, J = 9.0 Hz), 5.91 (dd, 1H, J = 15.6, 1.6 Hz), 6.51–6.54 (m, 2H), 6.85 (dd, 1H, J = 15.7, 5.1 Hz), 7.34 (bs, 5H). HRMS calcd for $C_{29}H_{42}N_4O_7$+Na, 581.2951, found 581.2937. Anal ($C_{29}H_{42}N_4O_7$•0.5 H_2O) C, H, N.

Example 21 - Preparation of Compound 22: N-Methoxy, N-Methyl-3-[CBZ-L-Leu L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenamide.

Preparation of Intermediate 3-[BOC-L-(Tr-*Gln*)]-E-Propenoic Acid.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (1.874 g, 3.46 mmol) was taken up in 20 mL EtOH, and 1N aq NaOH (7.95 mL, 7.95 mmol) was added dropwise via an addition funnel over 2 h. The resulting solution was stirred at room temperature for 1.5 h, whereupon the reaction mixture was poured into water and washed with ether. The aqueous layer was acidified to pH 3 with 1N HC1, and extracted 3 times with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated to provide 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (1.373 g, 77%) as a glassy off-white solid. No further purification was needed: IR (KBr) 3315, 1698, 1666 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.42 (s, 9H), 1.76 (m, 1H), 1.83–1.98 (m, 1H), 2.37 (t, 2H, J = 7.0 Hz), 4.30 (m, 1H), 4.88 (m, 1H), 5.85 (d, 1H, J = 15.3 Hz), 6.86 (dd, 1H, J = 15.5, 5.1 Hz), 6.92 (s, 1H), 7.25 (m, 15H).

Preparation of Intermediate N-Methoxy-N-Methyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenamide.

This intermediate was prepared from 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid and *N*, *O*-dimethylhydroxylamine hydrochloride as described in Example 1 for the synthesis of intermediate BOC-L-(Tr-*Gln*)-N(OMe)Me. This intermediate can alternatively be prepared by the reaction of BOC-L-(Tr-glutaminal) with

N-methoxyl-N-methyl-(2-triphenylphosphoranylidene)-acetamide in THF as described for the preparation of ethyl-3- [cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, or by the reaction of BOC-L-(Tr-glutaminal) with the anion of diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate as described in Example 6 for the preparation of 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone. IR (thin film) 3307, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.80 (m, 1H), 1.95 (m, 1H), 2.36-2.40 (m, 2H), 3.24 (s, 3H), 3.67 (s, 3H), 4.31 (m, 1H), 4.83 (m, 1H), 6.48 (d, 1H, J = 15.6 Hz), 6.79 (dd, 1H, J = 15.6, 5.6 Hz), 6.92 (m, 1H), 7.19-7.32 (m, 15H). HRMS calcd for $C_{33}H_{39}N_3O_5$+Cs, 690.1944, found 690.1967.

Preparation of Intermediate
N-Methoxy-N-Methyl-3-[BOC-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(Tr-*Gln*)]-E-propenamide (0.24 g, 0.49 mmol) was deprotected and coupled to BOC-L-(3R-phenyl)-Pro (0.14 g, 0.49 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide N-methoxy-N-methyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.22 g, 63%) as a white solid foam after column chromatography on silica (3% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.48 (m, 1H), 1.73 (m, 1H), 1.91-2.02 (m, 2H), 2.25 (m, 1H), 2.35-2.45 (m, 2H), 3.22 (s, 3H), 3.43-3.46 (m, 2H), 3.61-3.72 (m, 4H), 4.20 (m, 1H), 4.70 (m, 1H), 6.44 (m, 1H), 6.74 (m, 1H), 6.99 (m, 1H), 7.16 - 7.33 (m, 20H). MS calcd for $C_{44}H_{50}N_4O_6$+Na 753, found 753.

Preparation of Intermediate N-Methoxy-N-Methyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.18 g, 0.26 mmol) was deprotected and coupled to CBZ-L-Leu (0.070 g, 0.26 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide N-methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.076 g, 33%) as a clear glass after column chromatography on silica (3% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.79–0.93 (m, 6H), 1.01 (m, 1H), 1.22 (m, 1H), 1.40 (m, 1H), 1.51–1.95 (m, 2H), 2.01 (m, 1H), 2.19 (m, 1H), 2.31–2.52 (m, 2H), 3.15–3.20 (m, 3H), 3.53–3.68 (m, 6H), 3.92 (m, 1H), 4.08 (m, 1H), 4.57 (m, 1H), 5.02–5.15 (m, 2H), 6.25–6.35 (m, 2H), 6.63 (m, 1H), 7.15–7.35 (m, 25H). MS calcd for $C_{53}H_{59}N_5O_7$+H 878, found 878.

Preparation of Product -
N-Methoxy-N-Methyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenamide.

N-Methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.076 g, 0.090 mmol) was deprotected using the procedure described in Example 1 for the synthesis of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide N-methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-*Gln*]-E-propenamide (12.0 mg, 21%) as a clear glass after column chromatography (5% methanol/$CHCl_3$). IR (thin film) 3290, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.7 Hz), 1.44–1.74 (m, 3H), 2.05 (m, 1H), 2.15–2.22 (m, 2H), 2.32 (m, 1H), 2.41 (m, 1H), 3.21 (m,

1H), 3.51–3.74 (m, 5H), 4.14 (m, 1H), 4.23 (m, 1H), 4.62–4.66 (m, 2H), 5.09–5.10 (m, 2H), 5.27 (m, 1H), 5.48 (d, 1H, J = 13.8 Hz), 6.17 (d, 1H, J = 9.0 Hz), 6.36 (d, 1H, J = 15.3 Hz), 6.59 (m, 1H), 6.65 (dd, 1H, J = 15.6, 5.9 Hz), 7.21 (m, 1H), 7.24–7.35 (m, 10H). HRMS calcd for $C_{34}H_{45}N_5O_7$+Cs 768.2373, found 768.2395.

Example 22 - Preparation of Compound 24: Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Preparation of intermediate Ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

A solution of HCl in 1,4-dioxane (4.5 mL of a 4.0 M solution) was added to a solution of ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.39 g, 0.61 mmol) in the same solvent (4.5 mL) at room temperature. The reaction mixture was stirred for 2 h at rt and then concentrated. The resulting foamy solid was dissolved in dry CH_2Cl_2, and BOC-L-Leu (0.14 g, 0.61 mmol), l-hydroxybenzotriazole hydrate (0.12 g, 0.92 mmol), 4-methylmorpholine (0.27 mL, 2.45 mmol), and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.18 g, 0.92 mmol) were added sequentially. The reaction mixture was stirred for 12 h at 23 °C, and then it was partitioned between 1N HCl and CH_2Cl_2. The organic layer was washed with aq sat solution of $NaHCO_3$, dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel (2 % MeOH/$CHCl_3$) to provide ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 68%) as a foamy white solid. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.92 (d, 3H, J = 6.5 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.43 (s, 9H), 1.63–1.72 (m, 3H), 1.97–2.09 (m, 6H), 3.52 (m, 1H), 3.75 (m, 1H), 4.14–4.21 (m, 2H), 4.27 (m, 1H), 4.42–4.52 (m, 2H), 4.86 (m,

1H), 5.85 (dd, 1H, J = 15.6, 1.6 Hz), 6.75–6.82 (m, 2H), 7.07 (s, 1H), 7.19–7.32 (m, 15H). MS calcd for $C_{44}H_{56}N_4O_7$+Cs 885, found 885.

Preparation of Intermediate Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)] - E-Propenoate.

A solution of anh HCl in 1,4-dioxane (3.0 mL of a 4.0 M solution) was added to a solution of ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 0.42 mmol) in 3 mL 1,4-dioxane at 23°C. The reaction mixture was stirred for 2 h at 23°C, and it was then concentrated. The resulting foamy white solid was dissolved in dry CH_2Cl_2 and diisopropylethylamine (0.16 mL, 0.91 mmol), and ethylchlorothiolformate (0.052 mL, 0.91 mmol) were added sequentially. The reaction mixture was poured into H_2O, extracted with CH_2Cl_2 twice, and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography on silica gel (2% MeOH/$CHCl_3$) to provide ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 78%) as a glassy white foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.7 Hz), 0.91 (d, 3H, J = 6.7 Hz), 1.27 (t, 6H, J = 7.4 Hz), 1.34 (m, 1H), 1.70–1.72 (m, 2H), 1.96–2.10 (m, 6H), 2.37–2.42 (m, 2H), 2.88 (dd, 2H, J = 14.6, 7.5 Hz), 3.54 (m, 1H), 3.72 (m, 1H), 4.18 (dd, 2H, J = 14.3, 7.2 Hz), 4.25 (m, 1H), 4.52 (m, 1H), 4.75 (m, 1H), 5.78 (m, 1H), 5.85 (dd, 1H, J = 15.8, 1.8 Hz), 6.79 (dd, 1H, J = 15.8, 5.2 Hz), 6.88 (d, 1H, J = 8.1 Hz), 7.11 (s, 1H), 7.20–7.33 (m, 15H). MS calcd $C_{42}H_{52}N_4O_6S$+Cs 873, found 873.

Preparation of Product -Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Trifluoroacetic acid (2.0 mL) was added to a solution of ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 0.32 mmol) in chloroform (2.0 mL) and stirred at 23 °C for 1 h. The yellow solution evaporated to dryness, and the residue was purified by column chromatography on silica gel (5% MeOH/CHl_3) to provide ethyl-3-(ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-propenoate (0.096 g, 60%) as a glassy white foamy solid. IR (thin film) 3292, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, J = 6.5), 0.98 (d, 3H, J = 6.7 Hz), 1.29 (t, 6H, J = 7.4 Hz), 1.46-1.51 (m, 2H), 1.69-1.79 (m, 3H), 2.00-2.34 (m, 6H), 2.86-2.94 (m, 2H), 3.62 (m, 1H), 3.80 (m, 1H), 4.20 (dd, 2H, J = 14.3, 7.2 Hz), 4.42 (m, 1H), 4.65 (m, 1H), 4.80 (m, 1H), 5.57 (m, 1H), 5.93 (dd, 1H, J = 15.8, 1.5 Hz), 6.41 (m, 1H), 6.49 (m, 1H), 6.86 (dd, 1H, J = 15.8, 5.2 Hz), 7.06 (d, 1H, J = 8.7 Hz). HRMS calcd for $C_{23}H_{38}N_4O_6S$+Cs 499.2590, found 499.2596; Anal ($C_{23}H_{38}N_4O_6S$) C, H, N.

Example 23 - Preparation of Compound 25: Ethyl-3-[CBZ-L-Leu-L-Pip-L-*Gln*]-E-Propenoate.

Preparation of Intermediate CBZ-L-Leu-L-Pip-OtBu.

A suspension of CBZ-L-Pip-OtBu (0.52 g, 1.6 mmol) and Pd on C (10%, 0.10 g) in EtOAc was stirred under a hydrogen atmosphere (balloon) for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The resulting oil was coupled with CBZ-L-Leu (0.43 g, 1.6 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide CBZ-L-Leu-L-Pip-OtBu (0.57 g, 83%) as a colorless oil after column chromatography on silica

(20% EtOAc/hexanes): IR (thin film) 3300, 1726, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 6.5 Hz), 1.03 (d, 3H, J = 6.5 Hz), 1.46 (s, 9H), 1.50–1.60 (m, 2H), 1.64–1.83 (m, 2H), 2.23–2.27 (m, 2H), 3.19–3.28 (m, 2H), 3.77–3.81 (m, 2H), 4.76–4.83 (m, 2H), 5.10 (s, 2H), 5.26 (d, 1H, J = 4.7 Hz), 5.60 (d, 1H, J = 8.7 Hz), 7.27–7.36 (m, 5H); Anal. ($C_{24}H_{36}N_2O_5$) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Pip.

Trifluoroacetic acid (3 mL) was added to a solution of CBZ-L-Leu-L-Pip-OtBu (0.57 g, 1.3 mmol) in CH_2Cl_2 (6 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 1.5 h after which CCl_4 (6 mL) was added. The volatiles were then removed under reduced pressure to afford crude CBZ-L-Leu-L-Pip as a colorless oil. The crude acid thus obtained was immediately utilized in the following coupling procedure.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.36 g, 0.67 mmol) was deprotected and coupled with CBZ-L-Leu-L-Pip (0.26 g, 0.67 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenoate (0.20 g, 37%) as a foamy white solid: IR (thin film) 3304, 2954, 1713, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.86 (d, J = 6.5 Hz), 0.94–0.99 (m), 1.22–1.30 (m), 1.32–1.40(m), 1.43–1.50 (m), 1.62–1.68 (m), 1.79–1.98 (m), 2.26–2.45 (m), 3.25 (bs), 3.63–3.77 (m), 4.09–4.21(m), 4.50–4.58 (m), 4.73–4.78 (m), 4.88–5.10 (m), 5.27 (d, J = 7.2 Hz), 5.49 (d,

$J = 8.7$ Hz), 5.82 (dd, $J = 15.6$, 1.3 Hz), 5.90 (d, $J = 15.6$ Hz), 6.75 (d, $J = 5.3$ Hz), 6.79-6.88(m), 7.02-7.36(m); Anal. ($C_{48}H_{56}N_4O_7$) C, H, N.

Preparation of Product-Ethyl-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenoate (0.16 g, 0.18 mmol) was deprotected using the procedure described in Example 1 for the synthesis of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-propenoate (0.082 g, 83%) as a foamy white solid: IR (thin film) 3306, 1713, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.90-1.00(m), 1.23-1.30 (m), 1.41-2.08 (m), 2.12-2.22 (m), 2.44-2.59 (m), 3.41-3.48 (m), 3.80-3.84 (m), 4.12-4.22 (m), 4.54-4.60 (m), 4.79 (bs), 4.99-5.12 (m), 5.79-5.98 (m), 6.11(s), 6.27 (s), 6.79-6.92 (m), 7.14 (d, $J = 7.2$ Hz), 7.28-7.34 (m), 7.75 (d, $J = 7.8$ Hz). Anal. ($C_{29}H_{42}N_4O_7$•0.5 H_2O) C, H, N.

Example 24 - Preparation of Compound 26: 1-[1', 2'-Oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenone.

Preparation of Intermediate 1,2-Isooxazinane-2-Carboxylic Acid Ethyl Ester.

1,4 Dibromobutane (2.84 mL, 24.0 mmol), N-hydroxyurethane (5.0 g, 48.0 mmol), and KOH (2.67 g, 48.0 mmol) were taken up in 27 mL of EtOH and refluxed for 6 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (50% EtOAc/hexanes) to provide 1,2-isooxazinane-2-carboxylic acid ethyl ester (2.38 g, 68%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.31

(t, 3H, $J = 7.0$ Hz), 1.69–1.81 (m, 4H), 3.69 (t, 2H, $J = 5.5$ Hz), 3.98 (t, 2H, $J = 5.3$ Hz), 4.20–4.27 (m, 2H).

Preparation of Intermediate 1,2-Isooxazinane•HCl salt

1,2-Isooxazinane-2-carboxylic acid ethyl ester (2.38 g, 15.0 mmol) was refluxed in concentrated HCl for 3 h. The reaction mixture was cooled to rt and washed with Et_2O. The organic phase was discarded, and the aqueous layer was concentrated in vacuo. Traces of H_2O were removed by adding EtOH and reconcentrating. This yielded the HCl salt of 1,2-isooxazinane as a white solid (1.70 g, 92%) which was dried before subsequent use. ^1H NMR (CD_3OD) δ 1.86–1.90 (m, 2H), 1.96–2.02 (m, 2H), 3.52–3.46 (m, 2H), 4.25–4.29 (m, 2H), 4.88 (bs, 1H). MS calcd for $C_4H_{10}NO$ 87, found 87.

Preparation of Intermediate 1-[1', 2'-Oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-Propenone

1,2-Isooxazinane-HCl (0.12 g, 0.97 mmol) was coupled with 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (0.50 g, 0.97 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide 1-[1', 2'-oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-propenone (0.43 g, 76%) as a glassy white solid. ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.71–1.83 (m, 5H), 1.94 (m, 1H), 2.35–2.39 (m, 2H), 3.80–3.85 (m, 2H), 3.93–3.96 (m, 2H), 4.33 (m, 1H), 4.76 (m, 1H), 6.54 (d, 1H, $J = 15.3$ Hz), 6.79 (dd, 1H, $J = 15.6$, 5.6 Hz), 6.96 (m, 1H), 7.20–7.32 (m, 15H); MS calcd for $C_{35}H_{41}N_3O_5$+H 584, found 584.

Preparation of Intermediate 1-[1', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-Propenone.

1-[1', 2'-oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-propenone (0.36 g, 0.66 mmol) was deprotected and coupled with CBZ-L-Leu-L-Pip (0.26 g, 0.66 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide 1-[1', 2'-oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenone (0.14 g, 26%) as a foamy white solid: IR (thin film) 3301, 1658, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.86 (d, J = 6.9 Hz), 0.94-0.99 (m), 1.28-1.40 (m), 1.52-1.57 (m), 1.64-2.01(m), 2.27-2.55 (m), 3.27 (s, bs), 3.73-3.94 (m), 4.46-4.64 (m), 4.73-4.92 (m), 5.05 (s), 5.10 (s), 5.30 (s), 5.52 (d, J = 9.0 Hz), 6.48-6.61(m), 6.74-6.79 (m), 6.81-6.95 (m), 7.17-7.37 (m), 7.72 (d, J = 8.4 Hz).

Preparation of Product-1-[1', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenone.

1-[l', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenone (0.14 g, 0.17 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide 1-[1', 2'-oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-propenone (0.060 g, 59%) as a foamy white solid: IR (thin film) 3305, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.91 (d, J = 6.9 Hz), 0.94-0.97(m), 0.92 (d, J = 6.5 Hz), 1.26-1.82(m), 1.93-2.29(m), 2.45 (d, J = 12.1 Hz), 2.56-2.65 (m), 3.47 (s), 3.73-3.96 (m), 4.49-4.83 (m), 4.99 (s), 5.04 (s), 5.09 (s), 5.13 (s), 5.60-5.66(m), 5.72-5.85(m), 6.18(s), 6.31(s), 6.54-6.63 (m), 6.79-6.91(m), 7.14 (d, J = 7.8 Hz), 7.28-7.34 (m), 7.71 (d, J = 8.1 Hz). Anal. ($C_{31}H_{45}N_5O_7$) C, H, N.

Example 25 - Preparation of Compound 27: Ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-Propenoate.

Preparation of Intermediate FMOC-L-Leu-DL-(4-BOC)-Pipz.

To a suspension of DL-(4-BOC)-piperazine-3-carboxylic acid (0.20 g, 0.87 mmol) in dry CH_2Cl_2 (10 mL) was added 4-methylmorpholine (0.21 mL, 1.91 mmol) and trimethylsilylchloride (0.13 g, 1.04 mmol) at rt. A clear, homogeneous solution formed after ~2 h. To this solution was added the FMOC-L-Leu-Cl (0.32 g, 0.87 mmol) (Advanced ChemTech), and the mixture was stirred at rt overnight. At this time, the reaction mixture was poured into H_2O and extracted twice with CH_2Cl_2, dried over $MgSO_4$, and concentrated to provide FMOC-L-Leu-DL-(4-BOC)-Pipz (0.45 g, 91%) as a pale yellow foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.87–1.04 (m, 6H), 1.44 (s, 9H), 1.51 (m, 1H), 1.74 (m, 1H), 2.89–3.10 (m, 2H), 3.67 (m, 1H), 4.03 (m, 1H), 4.21–4.42 (m, 7H), 4.56–4.77 (m, 3H), 7.25–7.77 (m, 8H). MS calcd for $C_{31}H_{39}N_3O_7$+Cs, 698, found 698.

Preparation of Intermediate Ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)] -E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.59 g, 1.23 mmol) was deprotected and coupled to FMOC-L-Leu-DL-(4-BOC)-Pipz (0.70 g, 1.23 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.60 g, 49 %) as a white foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.87–1.03 (m, 6H), 1.18–1.30 (m, 3H), 1.44 (s, 9H), 2.00 (m, 1H), 2.24 (m ,1H), 2.38 (m, 1H), 3.06–3.13 (m, 2H), 3.69–3.77 (m, 2H), 3.89 (m, 1H), 4.07–4.24 (m, 6H), 4.33–4.59 (m, 9H),

5.85 (m, 1H), 6.75–6.88 (m, 2H), 7.19–7.78 (m, 23H). MS calcd for $C_{59}H_{67}N_5O_9$+Cs 1122, found 1122.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)] E-Propenoate.

To a solution of ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.60 g, 0.60 mmol) in $CHCl_3$ was added 4-(aminomethyl)piperidine (5 mL) at rt. The reaction mixture was stirred for 1 h and then sequentially washed twice with sat brine, 5 times with 10% aq K_2HPO_4 buffer (pH 5.5), and once with a sat solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated. The resulting oil (0.34 g, 0.44 mmol) was dissolved in dry CH_2Cl_2 (30 mL). 4-Methylmorpholine (0.24 g, 2.20 mmol) was added followed by benzylchloroformate (0.13 g, 0.88 mmol), and the mixture was stirred for 4 h at rt. This mixture was then poured into H_2O and extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (5% MeOH/$CHCl_3$) providing ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 77 %) as a white solid foam. ^1H NMR ($CDCl_3$) δ 0.82–1.00 (m, 6H), 1.23–1.28 (m, 3H), 1.40–1.58 (m, 2H), 1.67 (m, 1H), 1.98 (m, 1H), 2.26 (m, 1H), 2.37 (m, 1H), 2.75 (m, 1H), 3.07–3.11 (m, 2H), 3.50–4.06 (m, 4H), 4.13 - 4.20 (m, 2H), 4.52–5.15 (m, 6H), 5.87 (m, 1H), 6.75–7.03 (m, 2H), 7.08–7.41 (m, 20H). MS calcd for $C_{52}H_{63}N_5O_9$+Cs 1034, found 1034.

Preparation of Product Ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-Propenoate.

The BOC and trityl protecting groups were both removed from ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.10 g, 0.11 mmol) with trifluoroacetic acid as described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-propenoate (24.0 mg, 39 %) as a solid white foam. IR (thin film) 3308, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91-1.01 (m, 6H), 1.24-1.30 (m, 3H), 1.49 (m, 1H), 1.59 (m, 1H), 1.65-1.86 (m, 3H), 1.98 (m, 1H), 2.15-2.24 (m, 2H), 2.67-2.75 (m, 2H), 3.06 (m, 1H), 3.30 (m, 1H), 3.72-3.82 (m, 2H), 4.14-4.21 (m, 2H), 4.57-4.64 (m, 2H), 5.01-5.13 (m, 3H), 5.58 (m, 1H), 5.76 (d, 1H, J = 6.5 Hz), 5.90-5.98 (m, 2H), 6.88 (dd, 1H, J = 15.6, 5.6 Hz), 7.33 (s, 10H), 7.60 (d, 1H, J = 7.2 Hz). HRMS calcd for $C_{28}H_{41}N_5O_7$+Cs 692.2062, found 692.2040.

__Example 26 - Preparation of Compound 28:__
__Ethyl-3-(CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-*Gln*]-E-Propenoate.__

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-(Tr-*Gln*)]-E-Propenoate.

A solution of anh HCl in 1,4-dioxane (3.0 mL of a 4.0 M solution) was added to a solution of ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 0.20 mmol) in 1,4-dioxane (3.0 mL) at rt. The reaction mixture was stirred for 2 h at rt, and then concentrated under vacuum. The resulting foamy residue was taken up in EtOAc, washed with a sat $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The resulting yellow oil was dissolved in 3.0 mL of DMF. To this solution was added NaH

(5.0 mg, 0.20 mmol), followed by benzyl bromide (0.024 mL, 0.20 mmol) after a few minutes. The reaction mixture was stirred at rt overnight. The mixture was then concentrated under vacuum and 10 mL H_2O was added to the residue. CH_2Cl_2 was used to extract the aq. phase twice, which was dried over $MgSO_4$, concentrated, and purified using prep TLC (5% MeOH/$CHCl_3$), providing ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.10 g, 56 %) as a yellow foamy solid. ^1H NMR ($CDCl_3$) δ 0.82-0.94 (m, 6H), 1.21-1.32 (m, 4H), 1.48-1.66 (m, 3H), 1.97-2.13 (m, 2H), 2.25-2.35 (m, 2H), 2.81 (m, 1H), 3.38-3.52 (m, 3H), 3.64-3.76 (m, 3H), 4.14-4.24 (m, 2H), 4.46-5.22 (m, 6H), 5.96 (m, 1H), 6.75-7.04 (m, 2H), 7.15-7.35 (m, 25H), 7.51 (m, 1H). MS calcd for $C_{54}H_{61}N_5O_7$+H 892, found 892.

Preparation of Product-Ethyl-3-[CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.090 g, 0.10 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-*Gln*]-E-propenoate (0.030 g, 45 %) as a solid white foam. IR (thin film) 3323, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94-0.99 (m, 6H), 1.27-1.32 (m, 3H), 1.48 (m, 1H), 1.56 (m, 1H), 1.71-2.17 (m, 6H), 2.83 (m, 1H), 3.37-3.50 (m, 2H), 3.68-3.72 (m, 2H), 4.19-4.24 (m, 3H), 4.60-4.70 (m, 2H), 5.00-5.28 (m, 2H), 5.61-5.92 (m, 4H), 6.03 (m, d, 1H, J = 15.6 Hz), 6.87-6.92 (m, 2H), 7.26-7.32 (m, 10H), 7.78 (m, 1H). HRMS calcd for $C_{35}H_{47}N_5O_7$+Cs 782.2530, found 782.2546.

Example 27 - Preparation of Compound 29: Ethyl-3-[CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-Propenoate.

A solution of anh HC1 in 1,4-dioxane (2.5 mL of a 4.0 M solution) was added to a solution of ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.16 g, 0.18 mmol) in 1,4-dioxane (2.5 mL) at room temperature. The reaction mixture was stirred for 2 h at rt, and then it was concentrated under vacuum. The resulting foam was dissolved in dry CH_2C1_2, and phenylsulfonyl chloride (0.046 mL, 0.36 mmol) and 4-methylmorpholine (0.10 mL, 0.91 mmol) were added at rt and stirred for 2 h. The reaction mixture was poured into H_2O and extracted twice with CH_2C1_2. The organic layer was dried over $MgSO_4$ and concentrated to give a residue that was purified by column chromatography on silica gel (5% MeOH/$CHC1_3$) to provide ethyl-3-[CBZ-L-Leu-DL-(4-phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.057 g, 33%) as an off-white foamy solid. ^{1}H NMR ($CDC1_3$) δ 0.86-0.93 (m, 6H), 1.25-1.32 (m, 3H), 1.48 (m, 1H), 1.63 (m, 1H), 2.25-2.36 (m, 4H), 3.52 (m, 1H), 3.71-3.78 (m, 4H), 4.12-4.25 (m, 4H), 4.45 (m, 1H), 4.64 (m, 1H), 4.92-5.39 (m, 5H), 5.94 (m, 1H), 6.34 (m, 1H), 7.18-7.31 (m, 20H), 7.48-7.67 (m, 5H), 7.77 (m, 1H). MS calcd for $C_{53}H_{59}N_5O_9S+Cs$ 1074, found 1074.

Preparation of Product Ethyl-3-(CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-*Gln*)]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-DL-(4-phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.057 g, 0.06 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide

ethyl-3-[CBZ-L-Leu-DL- (4-phenylsulfonyl)-Pipz-L-*Gln*)]-E-propenoate (22.0 mg, 52%) as a white foamy solid. IR (thin film) 3322, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89–0.98 (m, 6H), 1.22–1.33 (m, 3H), 1.52 (m, 1H), 2.19–2.51 (m, 4H), 3.68–3.78 (m, 5H), 4.14–4.25 (m, 4H), 4.59–4.63 (m, 2H), 5.03–5.11 (m, 3H), 5.21 (m, 1H), 5.43 (m, 1H), 5.57 (m, 1H), 5.94 (m, 1H), 6.85 (m, 1H), 7.20–7.34 (m, 5H), 7.55–7.62 (m, 3H), 7.74–7.80 (m, 2H). HRMS calcd for $C_{34}H_{45}N_5O_9S+Cs$ 832.1992, found 832.1982.

Example 28 - Preparation of Compound 32:
Ethyl-3-(L-N-[(1,3-Dihydro-imidazol-2-one)- *Phe*]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate
Ethyl-3-[L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-Propenoate.

A solution of Phe-OtBu•HCl (0.77 g, 2.99 mmol) and triethylamine (0.833 mL, 5.98 mmol) in CH_2Cl_2 (10 mL) was added via cannula to a solution of triphosgene (0.295 g, 0.994 mmol) in CH_2Cl_2 (25 mL) at 23°C. The reaction mixture was stirred at that temperature for 5 min, and then it was heated to reflux for 1 h. After cooling to 23°C, a solution of aminoacetaldehyde dimethyl acetal (0.314 g, 2.99 mmol) and triethylamine (0.417 mL, 2.99 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The reaction mixture was stirred for 3 h at 23°C and then partitioned between half-saturated NH_4Cl (100 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided the intermediate urea as a colorless oil (0.36 g, 34%).

This material was dissolved in CH_2Cl_2 (20 mL) at 23°C. Trifluoroacetic acid (10 mL) was added, and the reaction mixture was stirred at 23°C for 1 h and then concentrated under reduced pressure. The resulting oil was partitioned between 10% NaOH (100 mL) and Et_2O (2 x 100 mL). The aqueous layer was acidified with concentrated HCl to pH = 2 (as indicated by pH paper) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude L-N-(1,3-dihydro-imidazol-2-one)-Phe (0.125 g, 53%) as a white solid. This material was dissolved in DMF (10 mL) and crude ethyl-3-[L-(Tr-*Gln*)]-E-propenoate•HCl (0.603 mmol) (generated as described in the first deprotection step in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), 1-hydroxybenzotriazole hydrate (0.122 g, 0.903 mmol), 4-methylmorpholine (0.2 mL, 1.81 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.173 g, 0.903 mmol) were added sequentially, and the reaction mixture was stirred for 18 h at 23°C and then concentrated under reduced pressure. The resulting oil was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided ethyl-3-[L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.129 g, 33%) as a solid yellow foam: R_f = 0.42 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3265, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.2), 1.68-1.78 (m, 1H), 1.89-1.95 (m, 1H), 2.27-2.33 (m, 2H), 3.06 (dd, 1H, *J* = 13.6, 7.3), 3.27 (dd, 1H, *J* = 13.6, 8.4), 4.18 (q, 2H, *J* = 7.2), 4.38 (bs, 1H), 4.96-5.02 (m, 1H), 5.62 (dd, 1H, *J* = 15.7,

1.6), 5.87–5.89 (m, 1H), 6.51–6.53 (m, 1H), 6.62 (dd, 1H, J = 15.7, 5.6), 6.90 (s, 1H), 7.00–7.33 (m, 20H), 7.79 (d, 1H, J = 7.5), 8.06 (s, 1H).

Preparation of Product - Ethyl-3-(L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Ethyl-3-[L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.129 g, 0.196 mmol) was deprotected according to the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate. Ethyl-3-(L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-propenoate (0.037 g, 46%) was isolated as a solid beige foam after removal of organic solvents and trituration with 4:1 Et_2O:CH_3CN, followed by filtration and washing with 2 x 10 mL Et_2O and air drying. R_f = 0.15 (10% CH_3OH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.22 (t, 3H, J = 7.2), 1.61–1.80 (m, 2H), 2.01–2.07 (m, 2H), 3.01–3.17 (m, 2H), 4.11 (q, 2H, J = 7.2), 4.32–4.41 (m, 1H), 4.87–4.92 (m, 1H), 5.68 (dd, 1H, J = 15.7, 1.4), 6.24–6.26 (m, 1H), 6.63–6.72 (m, 2H), 6.74 (s, 1H), 7.12–7.25 (m, 6H), 8.44 (d, 1H, J = 8.1), 9.83 (s, 1H); Anal. ($C_{21}H_{26}N_4O_5$•0.5 H_2O) C, H, N.

Example 29 - Preparation of Compound 33: Ethyl-3-(CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate 1-CBZ-2-(2,2-Dimethoxyethyl)-Hydrazine.

Aminoacetaldehyde dimethyl acetal (0.430 g, 3.95 mmol) was added to a solution of N-CBZ-3-phenyl-oxaziridine (1.11 g, 4.35 mmol) (prepared as described in *Tetrahedron Lett.* **1993**, 6859, the disclosure of which is entirely incorporated herein by reference) in CH_2Cl_2 (20 mL) at 23°C. The resulting yellow solution was stirred at

23°C for 18 h, and it then was concentrated under reduced pressure. Purification of the residue by flash column chromatography (3% CH_3OH/CH_2Cl_2) provided 1-CBZ-2-(2,2-dimethoxyethyl)-hydrazine (0.434 g, 43%) as a pale yellow oil: R_f = 0.40 (5% CH_3OH/CH_2Cl_2); IR (thin film) 3317, 1721, 1456 cm^{-1}; ^{1}H NMR (C_6D_6) δ 2.96 (bs, 2H), 3.06 (bs, 6H), 3.97 (bs, 1H), 4.37 (bs, 1H), 4.97 (bs, 2H), 5.87 (bs, 1H), 6.98-7.18 (m, 5H).

Preparation of Intermediate Ethyl-3-[CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-Propenoate.

A solution of Phe-OtBu•HCl (0.440 g, 1.71 mmol) and triethylamine (0.345 mL, 2.47 mmol) in CH_2Cl_2 (20 mL) was added via cannula to a solution of triphosgene (0.168 g, 0.566 mmol) in CH_2Cl_2 (40 mL) at 23°C. The reaction mixture was stirred at that temperature for 5 min, and then it was heated to reflux for 1 h. After cooling to 23°C, a solution of 1-CBZ-2-(2,2-dimethoxyethyl)-hydrazine (0.434 g, 1.71 mmol) and triethylamine (0.173 mL, 1.24 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The reaction mixture was stirred for 1 h at 23°C, and then it was partitioned between half-saturated NH_4Cl (100 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (3% CH_3OH/CH_2Cl_2) provided the intermediate urea as a colorless oil (0.56 g, 65%). This material was dissolved in CH_2Cl_2 (20 mL) at 23°C. Trifluoroacetic acid (10 mL) was added, and the reaction mixture was stirred at 23°C for 1.5 h. CCl_4 (10 mL) was added, and the mixture was concentrated under reduced pressure. The resulting oil was partitioned between 10% NaOH (100 mL) and Et_2O (2 x 100 mL). The

aqueous layer was acidified with concentrated HC1 to pH = 2 (as indicated by pH paper) and was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude CBZ-amino-L-N-(1,3-dihydro-imidazol-2-one)-*Phe* (0.374 g, 89%) as a solid white foam. This material was dissolved in CH_2Cl_2 (10 mL) and crude ethyl-3-[L-(Tr-*Gln*)]-E-propenoate•HC1 (0.981 mmol) (generated as described in the first deprotection step in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), 1-hydroxybenzotriazole hydrate (0.172 g, 1.27 mmol), 4-methylmorpholine (0.323 mL, 2.94 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.244 g, 1.27 mmol) were added sequentially. The reaction mixture was stirred for 18 h at 23°C, and it then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided ethyl-3-[CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.449 g, 57%) as a solid white foam: R_f = 0.44 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3284, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 1H, J = 7.2), 1.42-1.44 (m, 1H), 2.00-2.16 (m, 3H), 3.08 (dd, 1H, J = 13.4, 7.5), 3.32-3.39 (m, 1H), 4.01-4.18 (m, 3H), 4.47 (bs, 1H), 4.90 (bs, 2H), 4.99-5.04 (m, 1H), 5.60 (dd, 1H, J = 16.0, 1.6), 5.86 (bs, 1H), 6.54 (d, 1H, J = 3.1), 6.66 (dd, 1H, J = 16.0, 4.5), 6.94-7.32 (m, 26H), 7.83 (s, 1H); Anal. ($C_{48}H_{47}N_5O_7$•0.5 H_2O) C, H, N.

Preparation of Product Ethyl-3-(CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.147 g, 0.182 mmol) was deprotected according to the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate. Ethyl-3-(CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-propenoate (0.042 g, 40%) was isolated as a white solid after removal of organic solvents and trituration with Et_2O, followed by filtration and washing with 2 x 10 mL Et_2O and air drying: mp = 216–218°C; R_f = 0.27 (10% CH_3OH/CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, J = 7.2), 1.61–2.06 (m, 2H), 2.01–2.06 (m, 2H), 3.11–3.13 (m, 2H), 3.36–3.38 (m, 1H), 4.11 (q, 2H, J = 7.2), 4.34–4.38 (m, 1H), 4.90–4.96 (m, 1H), 5.09 (bs, 2H), 5.66 (d, 1H, J = 15.7), 6.53 (d, 1H, J = 2.8), 6.69 (dd, 1H, J = 15.7, 5.6), 6.75–6.77 (m, 2H), 7.21 (bs, 6H), 7.37 (bs, 4H), 8.52 (d, 1H, J = 8.1), 10.14 (s, 1H); Anal. ($C_{29}H_{33}N_5O_7$) C, H, N.

**<u>Example 30 - Preparation of Compound 34:
Ethyl-3-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.</u>**

Preparation of Intermediate Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This material was prepared from ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.832 g, 1.53 mmol) and BOC-L-Val-L-N-Me-Phe (0.570 g, 1.51 mmol) using the method described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (gradient: 43%–50%

EtOAc in hexanes) as a white foam (0.789 g, 64%): IR (thin film) 3295, 1708, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 0.66–0.73 (m), 0.81 (d, J = 6.8 Hz), 0.86 (d, J = 6.8 Hz), 1.23–1.37 (m), 1.35 (s), 1.42 (s), 1.62–1.85 (m), 1.88–2.06 (m), 2.20–2.27 (m), 2.83–3.03 (m), 2.88 (s), 2.99 (s), 3.31 (dd, J = 14.0, 8.2 Hz), 3.41 (dd, J = 14.0, 5.8 Hz), 4.03–4.10 (m), 4.16 (q, J = 7.2 Hz), 4.17 (q, J = 7.2 Hz), 4.27–4.34 (m), 4.45–4.56 (m), 4.57–4.70 (m), 4.88–5.03 (m), 5.59 (d, J = 15.7 Hz), 5.87 (d, J = 15.7 Hz), 6.20 (d, J = 8.4 Hz), 6.66 (dd, J = 15.7, 5.1 Hz), 6.80 (dd, J = 15.7, 6.1 Hz), 6.89–7.05 (m), 7.12–7.34 (m), 7.88 (d, J = 8.1 Hz). Anal. ($C_{48}H_{58}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Intermediate Ethyl-3-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.366 g, 0.456 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.057 mL, 0.55 mmol) as described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (gradient: 44%-50% EtOAc in hexanes) as a white foam (0.217 g, 60%): IR (thin film) 3295, 1713, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 0.48 (d, J = 6.5 Hz), 0.71 (d, J = 6.8 Hz), 0.80–0.89 (m), 1.17–1.22 (m), 1.58–2.06 (m), 2.19–2.32 (m), 2.65–3.04 (m), 2.84 (s), 2.97 (s), 3.29–3.43 (m), 4.18 (q, J = 7.2 Hz), 4.49–4.59 (m), 4.65–4.71 (m), 4.75–4.83 (m), 5.65 (dd, J = 15.9, 1.6 Hz), 5.71–5.76 (m), 5.81–5.90 (m), 6.31–6.36 (m), 6.70 (dd, J = 15.9, 5.3 Hz),

6.79 (dd, J = 15.9, 5.9 Hz), 6.88 (s), 7.01(s), 7.12–7.34 (m), 7.75–7.80 (m). Anal. ($C_{46}H_{54}N_4O_6S$•0.5 H_2O) C, H, N.

Preparation of Product - Ethyl-3-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.187 g, 0.236 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give ethyl-3-(ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-propenoate after column chromatography (50% acetone in hexanes, then 6% MeOH in CH_2Cl_2) as a white foam (0.076 g, 58%): IR (thin film) 3307, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.47 (d, J = 6.5 Hz), 0.77 (d, J = 6.8 Hz), 0.92 (d, J = 6.5 Hz), 0.93 (d, J = 6.5 Hz), 1.25 (t, J = 7.2 Hz), 1.29 (t, J = 7.2 Hz), 1.42–1.54(m), 1.64–1.79(m), 1.80–2.03 (m), 2.08–2.31 (m), 2.73–3.01(m), 2.92 (s), 3.04–3.15 (m), 3.07 (s), 3.31–3.47 (m), 4.16–4.26 (m), 4.19 (q, J = 7.2 Hz), 4.51–4.65 (m), 4.70–4.78 (m), 5.72 (dd, J = 15.6, 1.6 Hz), 5.85–6.05 (m), 6.19 (bs), 6.56 (d, J = 8.1 Hz), 6.75 (dd, J = 15.6, 5.3 Hz), 6.80–6.89 (m), 7.15–7.35(m), 7.46 (d, J = 7.8 Hz). Anal. ($C_{27}H_{40}N_4O_6S$) C, H, N.

Example 31 - Preparation of Compound 35: Ethyl-3-(Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.365 g, 0.455 mmol) was deprotected and coupled with cyclopentyl chlorothiolformate (0.09 mL, about

0.5 mmol) using the procedure described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (40%-50% EtOAc in hexanes) as a white foam (0.231 g, 61%): IR (thin film) 3295, 1713, 1655, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.50 (d, J = 6.5 Hz), 0.73 (d, J = 6.8 Hz), 0.80-0.88 (m), 1.22-2.31 (m), 2.84-3.04 (m), 2.86 (s), 2.98 (s), 3.29-3.41 (m), 3.54-3.69 (m), 4.08-4.25 (m), 4.17 (q, J = 7.2 Hz), 4.48-4.63 (m), 4.67-4.82 (m), 5.64 (dd, J = 15.7, 1.6 Hz), 5.76-5.82 (m), 5.83-5.91 (m), 5.87 (dd, J = 15.7, 1.6 Hz), 6.39-6.45 (m), 6.70 (dd, J = 15.7, 5.3 Hz), 6.79 (dd, J = 15.7, 5.8 Hz), 6.93 (s), 7.06 (s), 7.12-7.33 (m), 7.72 (d, J = 7.8 Hz). Anal. ($C_{49}H_{58}N_4O_6S \cdot 0.5\ H_2O$) C, H, N.

Preparation of Product-
Ethyl-3-(Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.179 g, 0.215 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate to give ethyl-3-(cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-propenoate after column chromatography on silica gel (50% acetone in hexanes, then 6% MeOH in CH_2Cl_2) as a white foam (0.086 g, 68%): IR (thin film) 3295, 1713, 1666, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.48 (d, J = 6.5 Hz), 0.77 (d, J = 6.8 Hz), 0.92 (d, J = 6.5 Hz), 0.93 (d, J = 6.8 Hz), 1.29 (t, J = 7.2 Hz), 1.37-1.79 (m), 1.81-2.29 (m), 2.91-3.00 (m), 2.92 (s), 3.03-3.15 (m), 3.06 (s), 3.34 (dd, J = 14.0, 5.3 Hz), 3.43 (dd, J = 14.0, 6.7 Hz), 3.59-3.69 (m), 4.16-4.26 (m), 4.18 (q, J = 7.2 Hz),

4.52–4.65 (m), 4.68–4.77 (m), 5.72 (dd, J = 15.9, 1.6 Hz), 5.78 (bs), 5.85 (bs), 5.90 (dd, J = 15.6, 1.2 Hz), 6.01 (bs), 6.19 (bs), 6.42 (d, J = 8.1 Hz), 6.67 (d, J = 9.0 Hz), 6.75 (dd, J = 15.6, 5.3 Hz), 6.80–6.87 (m), 7.16–7.34 (m), 7.42 (d, J = 7.8 Hz). Anal. ($C_{30}H_{44}N_4O_6S$) C, H, N.

Example 32 - Preparation of Compound 36: N-Methoxy-N-Methyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenamide.

Preparation of Intermediate N-Methoxy-N-Methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(Tr-*Gln*)]-E-propenamide (0.29 g, 0.58 mmol) was deprotected and coupled to BOC-L-Leu-L-N-Me-Phe (0.23 g, 0.58 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide N-methoxy-N-methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.23 g, 47%) as a white solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.63–0.66 (m, 6H), 0.71 (m, 1H), 0.86–0.95 (m, 3H), 1.06 (m, 1H), 1.31–1.44 (m, 9H), 1.84 (m, 1H), 2.00 (m, 1H), 2.25–2.28 (m, 2H), 2.91–3.00 (m, 3H), 3.23 (s, 3H), 3.66–3.68 (m, 3H), 4.13 (m, 1H), 4.58 (m, 1H), 4.71 (m, 1H), 4.86 (m, 1H), 6.35 (m, 1H), 6.55 (m, 1H), 6.80 (m, 1H), 7.10–7.33 (m, 20H), 8.20 (d, 1H, J = 8.7 Hz). MS calcd for $C_{49}H_{61}N_5O_7$+Na 854, found 854.

Preparation of Intermediate N-Methoxy-N-Methyl 3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.098 g, 0. 13 mmol) was deprotected and treated with ethylchlorothiolformate (0.016 mL, 0.15 mmol) using the procedure described in Example 22 for the preparation of ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate, to provide N-methoxy-N-methyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.041 g, 39 %) as a clear glass. ^{1}H NMR ($CDCl_3$) δ 0.61–0.75 (m, 3H), 0.80–0.88 (m, 2H), 1.15–1.27 (m, 4H), 1.34–1.44 (m, 2H), 1.65–1.96 (m, 5H), 2.25–2.33 (m, 2H), 2.72–3.05 (m, 3H), 3.20 (s, 3H), 3.66 (s, 3H), 4.61 (m, 1H), 5.77 (dd, 1H, J = 17.4, 7.5 Hz), 6.49 (m, 1H), 6.83 (m, 1H), 7.12 (m, 1H), 7.19–7.33 (m, 20H), 8.01 (d, 1H, J = 8.1 Hz). MS calcd for $C_{47}H_{57}N_5O_6S$+Cs MS calcd for 952, found 952.

Preparation of Product N-Methoxy-N-Methyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenamide.

N-Methoxy-N-methyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.040 g, 0.049 mmol) was deprotected using the procedure described in Example 1 for the preparation ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate, to provide N-methoxy-N-methyl-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenamide (17.0 mg, 61%) as a white foam after column chromatography (2% methanol/$CHCl_3$). IR (thin film) 3274, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.63–0.64 (m, 3H), 0.91 (d, 2H, J = 6.2 Hz), 1.22–1.28 (m, 4H), 1.43 (m, 1H), 1.63 (m, 1H), 1.95–2.02 (m, 2H), 2.80–2.98 (m, 4H), 3.25 (s, 3H), 3.69–3.70 (m, 3H), 4.42 (m, 1H), 4.62–4.66 (m, 2H), 6.09 (m, 1H). 6.18 (dd, 1H, J = 15.0, 7.5 Hz), 6.57 (m, 1H),

6.82 (m, 1H), 7.15-7.34 (m, 7H), 7.89 (d, 1H, J = 8.4 Hz). HRMS calcd for $C_{28}H_{43}N_5O_6S$+Cs 710.1988, found 710.2014.

Example 33 - Preparation of Compound 30: Ethyl-3-([(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-{[(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-(Tr-*Gln*)}-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.39 g, 0.72 mmol) was deprotected and coupled with [(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid (0.28 g, 0.73 mmol) (prepared according to the procedure of C.A. Veale, et al., *J. Med. Chem.* **1995**, *38*, *98*, the disclosure of which is entirely incorporated herein by reference) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), to give ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-l-pyrimidinyl]-L-(Tr-*Gln*)}-E-propenoate (0.43 g, 73%) as a white solid after column chromatography on silica (3% methanol/$CHCl_3$): mp = 106-112°C; IR (thin film) 3297, 1722, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 1.76-1.86 (m, 1H), 1.93-2.04 (m, 1H), 2.36-2.52 (m, 2H), 4.07-4.30 (m, 5H), 4.51 (bs, 1H), 5.21 (s, 2H), 5.81 (dd, 1H, J = 15.6, 1.6 Hz), 6.73 (dd, 1H, J = 15.6, 4.8 Hz), 6.86 (s, 1H), 7.08-7.23 (m, 15 H), 7.29-7.54 (m, 11H), 8.73 (bs, 1H); Anal. ($C_{48}H_{45}N_5O_7$•1.0 H_2O) C, H, N.

Preparation of Product Ethyl-3-{[(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*}-E-Propenoate.

Ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]-L-(Tr-*Gln*)}-E-propenoate (0.22 g, 0.27 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate, to provide ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-l-pyrimidinyl]-L-*Gln*}-E-propenoate (0.12 g, 79%) as a white solid after removal of organic solvents and trituration with Et_2O, followed by filtration and washing with 2 x 10 mL Et_2O and air drying: mp = 200–205°C; IR (thin film) 3278, 1719, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 1.56–1.68 (m, 1H), 1.71–1.77 (m, 1H), 2.01–2.06 (m, 2H), 4.13 (q, 2H, J = 7.2 Hz), 4.39–4.55 (m, 3H), 5.18 (s, 2H), 5.78 (dd, 1H, J = 15.9, 1.6 Hz), 6.70–6.77 (m, 2H), 7.24 (s, 1H), 7.30–7.55 (m, 10H), 8.34 (d, 1H, J = 8.1 Hz), 8.45 (s, 1H), 8.94 (s, 1H); Anal. ($C_{29}H_{31}N_5O_7$•0.25 H_2O) C, H, N.

Example 34 - Preparation of Compound 31: Ethyl-3-{[(5-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*}-E-Propenoate.

Preparation of Product Ethyl-3-{[(5-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-Gln}-E-Propenoate.

Borontribromide (0.18 mL of a 1.0 M solution in CH_2Cl_2, 0.18 mmol) was added to a solution of ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-l-pyrimidinyl]-L-*Gln*}-E-propenoate (0.050 g, 0.089 mmol) in trifluoroacetic acid (4 mL) at 23°C. The reaction mixture was stirred for 2 h at 23°C, then it was quenched with EtOH (2 mL) and concentrated. The residue was then partitioned between $NaHCO_3$ (50 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and

concentrated to afford ethyl-3-{[(5-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]-L-*Gln*}-E-propenoate (0.013 g, 36%) as a white solid: mp = 175°C (dec); IR (thin film) 3421, 1646 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, 3H, *J* = 7.2 Hz), 1.62-1.64 (m, 1H), 1.71-1.78 (m, 1H), 2.01-2.06 (m, 2H), 4.13 (q, 2H, *J* = 7.2 Hz), 4.37-4.51 (m, 3H), 5.14 (bs, 1H), 5.79 (d, 1H, *J* = 15.6 Hz), 6.53-6.78 (m, 2H), 7.09-7.52 (m, 6H), 8.28 (d, 1H, *J* = 8.4 Hz).

Example 35 - Preparation of Compound 37: Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo [1,2-α]Pyrimidine-6-L-*Gln*]-E-Propenoate.

Preparation of Intermediate (S)-Pyrrolidin-2-one-5-Carboxylic Acid t-Butyl Ester.

To a suspension of L-pyroglutamic acid (2.00 g, 15.49 mmol) in t-butyl acetate was added 70% $HClO_4$ (0.46 mL, 17.04 mmol). The suspension was stirred at rt in a tightly closed flask overnight. The resulting solution was poured slowly into a sat. solution of $NaHCO_3$ and extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated to provide (S)-pyrrolidin-2-one-5-carboxylic acid t-butyl ester. (2.04 g, 85%) as a white solid· ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.16-2.48 (m, 4H), 4.14 (m, 1H), 5.97 (bs, 1H). MS calcd for $C_9H_{15}NO_3$+H 186, found 186.

Preparation of Intermediate (S)-Pyrrolidin-2-thione-5-Carboxylic Acid t-Butyl Ester.

To a solution of (S)-pyrrolidin-2-one-5-carboxylic acid t-butyl ester (2.04 g, 11.01 mmol) in benzene was added Lawesson's Reagent (2.22 g, 5.50 mmol). The reaction mixture was heated at reflux overnight, concentrated under vacuum, and purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to provide

(S)-pyrrolidin-2-thione-5-carboxylic acid t-butyl ester (1.75 g, 79%) as a tan solid. ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.30 (m, 1H), 2.53 (m, 1H), 2.85–3.04 (m, 2H), 4.42 (t, 1H, J = 7.7 Hz), 7.88 (bs, 1H). MS calcd for $C_9H_{15}NO_2S$+H 202, found 202.

Preparation of Intermediate (S)-2-Methylsulfanyl-3,4-Dihydro-5*H*-Pyrrole-5-Carboxylic Acid t-Butyl Ester.

To a solution of (S)-pyrrolidin-2-thione-5-carboxylic acid t-butyl ester (1.75 g, 8.71 mmol) in 35 mL of dry THF was added MeI (2.2 mL, 34.83 mmol) at rt. The mixture was stirred at rt for 3 h and concentrated under vacuum. CH_2Cl_2 was added to the resulting oil which was poured into a sat. solution of $NaHCO_3$. This was extracted 3 times with CH_2Cl_2, dried over $MgSO_4$, and concentrated to provide (S)-2-methylsulfanyl-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester (1.63 g, 87%) as a brown oil which was used without further purification. ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.09 (m, 1H), 2.28 (m, 1H), 2.48 (s, 3H), 2.56–2.80 (m, 2H), 4.59 (m, 1H). MS calcd for $C_{10}H_{17}NO_2S$+H, 216, found 216.

Preparation of Intermediate (S)-2-Amino-3,4-Dihydro-5*H*-Pyrrole-5-Carboxylic Acid t-Butyl Ester•HCl Salt.

To a solution of (S)-2-methylsulfanyl-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester (0.42 g, 1.95 mmol) in 4.0 mL anhydrous MeOH was added anh NH_4Cl (0.11 g, 2.05 mmol). The reaction mixture was heated to reflux for 2 h, concentrated in vacuo, and the residue was taken up in CH_2Cl_2. The white solids were filtered, and the filtrate was concentrated to provide (S)-2-amino-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester•HCl (0.41 g, 94%) as a light yellow solid. ^1H NMR ($CDCl_3$) δ 1.49 (s,

9H), 2.24 (m, 1H), 2.52 (m, 1H), 3.06-3.08 (m, 2H), 4.44 (m, 1H), 9.81-9.84 (m, 2H). MS calcd for $C_9H_{16}N_2O_2$+H 185, found 185.

Preparation of Intermediate (S)-4-Oxo-4,6,7,8-Tetrahydropyrrolo [1,2-*a*] Pyrimidine- 3,6-Dicarboxylic Acid 6-t-Butyl Ester 3-Methyl Ester.

A solution of freshly prepared sodium methoxide (Na, 50 % by weight in paraffin, 0.084 g, 1.84 mmol, 2.25 mL anh MeOH) was added slowly to a solution of (S)-2-amino-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester•HCl (0.41 g, 1.84 mmol) in 2.25 mL anh MeOH cooled to -10°C. After 1 h, the resulting white precipitate (NaCl) was filtered, and the solution of this free base was slowly added to a solution of dimethylmethoxymethylene malonate (0.32 g, 1.84 mmol) in 2.25 mL anh MeOH at -10°C. The reaction mixture was stirred at 0°C overnight at which time it was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (2% MeOH/$CHCl_3$) to afford (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester 3-methyl ester (0.22 g, 40 %) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.31 (m, 1H), 2.57 (m, 1H), 3.09-3.33 (m, 2H), 3.90 (s, 3H), 5.03 (m, 1H), 8.69 (s, 1H). MS calcd $C_{14}H_{18}N_2O_5$+H 295, found 295.

Preparation of Intermediate (S)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-3,6-Dicarboxylic Acid 6-t-Butyl Ester.

To a solution of (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester 3-methyl ester (0.22 g, 0.74 mmol) in MeOH cooled to 0°C was added 2N NaOH (0.37 mL, 0.74 mmol) dropwise. The reaction mixture was

allowed to warm slowly to rt and stirred overnight. The reaction mixture was washed twicewith Et_2O, and the aqueous layer was acidified to pH 2 with 1N HC1, which was then extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to provide (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester (0.14 g, 70%) as a solid yellow foam· ^{1}H NMR ($CDC1_3$) δ 1.50 (s, 9H), 2.41 (m, 1H), 2.68 (m, 1H), 3.21–3.41 (m, 2H), 5.10 (m, 1H), 8.94 (s, 1H). MS calcd $C_{13}H_{16}N_2O_5$+H, 281, found 281.

Preparation of Intermediate (S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-6-Carboxylic Acid t-Butyl Ester.

(S)-4-Oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester (0.58 g, 2.07 mmol), triethylamine (0.29 mL, 2.07 mmol) and diphenylphosphoryl azide (0.45 mL, 2.07 mmol) in 1,4-dioxane (10 mL) were heated to reflux for 2 h. Benzyl alcohol (0.24 mL, 2.28 mmol) was added and heating at reflux was continued for another 3 h. The reaction mixture was then concentrated under vacuum, and the residue was purified by column chromatography on silica gel (2% MeOH/$CHC1_3$) to provide (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid t-butyl ester (0.62 g, 77%) as a yellow solid. ^{1}H NMR ($CDC1_3$) δ 1.48 (s, 9H), 2.30 (m, 1H), 2.56 (m, 1H), 3.05–3.21 (m, 2H), 4.98 (m, 1H), 5.20 (s, 2H), 7.30–7.40 (m, 6H), 8.67 (bs, 1H). MS calcd for $C_{20}H_{23}N_3O_5$+H, 386, found 386.

Preparation of Intermediate (S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-6-Carboxylic Acid.

To (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid t-butyl ester (0.20 g, 0.52 mmol) was added 8.0 mL of a 1:1 solution of TFA:$CHCl_3$ with 3 drops of H_2O. The reaction mixture was stirred at rt overnight, at which time it was concentrated under vacuum. CCl_4 was added, and the mixture was reconcentrated, and then triturated in Et_2O. Filtration provided (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid (0.14 g, 82%) as a tan solid. ^{1}H NMR ($CDCl_3$) δ 2.50–2.63 (m, 2H), 3.16–3.29 (m, 2H), 5.13 (m, 1H), 5.20 (s, 2H), 5.45 (bs, 1H), 7.37 (s, 5H), 7.40 (s, 1H), 8.70 (bs, 1H). MS calcd for $C_{16}H_{15}N_3O_5$+H 330, found 330.

Preparation of Intermediate Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo[1,2-*a*]Pyrimidine-6-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.28 g, 0.52 mmol) was deprotected and coupled to (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid (0.14 g, 0.41 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[(S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-L-(Tr-*Gln*)]-E-propenoate (0.26 g, 83%) as a solid white foam after column chromatography (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 1.83 (m, 1H), 2.01 (m, 1H), 2.29–2.36 (m, 2H), 2.49–2.51 (m, 2H), 2.97 (m, 1H), 3.19 (m, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.53–4.57 (s, 2H), 5.86 (dd, 1H, J = 15.6, 1.6 Hz), 6.79

(dd, 1H, J = 15.6, 5.3 Hz), 6.89 (s, 1H), 7.16–7.37 (m, 21H), 7.53 (d, 1H, J = 7.2 Hz), 8.65 (bs, 1H)•MS calcd for $C_{44}H_{43}N_5O_7$+Cs, 886, found 886.

Preparation of Product-Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo[1,2-*a*]Pyrimidine-6-L-*Gln*]-E-Propenoate.

Ethyl-3-[(S)-3-(CBZ-amino)-4-oxo- 4,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyrimidine-6-L-(Tr-*Gln*)]-E-propenoate (0.25 g, 0.33 mmol) was deprotected using the procedure described in Example 22 for the preparation of ethyl-3-(ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-propenoate, to provide ethyl-3-[(S)-3-(CBZ-amino)-4-oxo4,6,7,8-tetrahydropyrrolo [1,2-*a*]pyrimidine-6-L-*Gln*]-E-propenoate (0.10 g, 59%) as a white solid after column chromatography on silica (5% methanol/$CHCl_3$): mp = 204°C (dec.); IR (thin film) 3282 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 1.86 (m, 1H), 2.05 (m, 1H), 2.28–2.35 (m, 2H), 2.46–2.51 (m, 2H), 3.02 (m, 1H), 4.20 (q, 2H, J = 7.2 Hz), 4.62 (m, 1H), 5.00 (dd, 1H, J = 8.3, 3.6 Hz), 5.20 (s, 1H), 5.57 (m, 1H), 5.86 (m, 1H), 5.94 (dd, 1H, J = 15.5, 1.4 Hz), 6.84 (dd, 1H, J = 15.6, 5.2 Hz), 7.36–7.40 (m, 5H), 7.44 (s, 2H), 8.69 (m, 1H). HRMS calcd for $C_{25}H_{29}N_5O_7$+Cs 644.112, found 644.1143; Anal ($C_{25}H_{29}N_5O_7$) C, H, N.

The remaining compounds illustrated above can be produced by the skilled artisan, using routine experimentation, in a manner analogous to the various procedures described above in Examples 1 through 35.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Inhibition of Rhinovirus Protease

Stock solutions (50 mM, in DMSO) of various compounds were prepared; dilutions were in the same solvent. Recombinant Rhinovirus 3C proteases from serotypes 14, 16, 2 or 89 were prepared by the following standard chromatographic procedures: (1) ion exchange using Q Sepharose Fast Flow from Pharmacia; (2) affinity chromatography using Affi-Gel Blue from Biorad; and (3) sizing using Sephadex G-100 from Pharmacia. Assays contained 2% DMSO, 50 mM tris pH 7.6, 1 mM EDTA, a compound at the indicated concentrations, approximately 1μM substrate, and 50-100 nM protease. For K_i determinations, the compound and the enzyme were preincubated for 10 minutes at 30°C prior to addition of the substrate (substrate start). The $k_{obs/I}$ values were obtained from reactions initiated by addition of enzyme rather than substrate. RVP activity is measured in the fluorescence resonance energy transfer assay. The substrate was (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Phe-Gln-Gly-Pro-Val-Gly)-EDANS. In the uncleaved peptide, the EDANS fluorescence was quenched by the proximal DABCYL moiety. When the peptide was cleaved, the quenching was relieved, and activity was measured as an increase in fluorescence signal. Data was analyzed using standard non linear fitting programs (Enzfit), and are shown Table 1.

TABLE 1

COMPOUND	RVP	INHIB	$k_{obs/I}$ ($M^{-1}sec^{-1}$)
1		>100μM(K_i)	52
2		ND	5,300
	(2)	ND	617

	(16)	ND	1,035
3		12μM(K_i)	16,565
	(2)	ND	292
	(16)	ND	929
4		2.9μM(K_i)	43,800
	(2)	ND	541
	(16)	ND	2,009
5		ND	17,320
6		ND	9,500
7		ND	3,824
8		ND	6,885
9		4.4μM(K_i)	57,000
10		2.0μM(K_i)	41,800
11		ND	12,000
12		ND	5,070
13		ND	355,800
	(2)	ND	3,980
	(16)	ND	11,680
14		0.8μM(K_i)	56,400
	(2)	ND	800
	(16)	ND	1800
15		2.5μM(K_i)	36,400
	(2)	ND	3,500
	(16)	ND	5,600
16		12μM(K_i)	8,300
	(2)	ND	600
	(16)	ND	1,000
17		ND	750,000
18		7.0μM(K_i)	423
19		ND	1,927

20		$62\mu M(K_i)$	3,332
21		$50\mu M(K_i)$	256
22		ND	100
23		$60\mu M(K_i)$	605
24		$8\mu M(K_i)$	21,960
	(2)	ND	7,100
	(16)	ND	9,300
25		ND	1,469
	(2)	ND	1,277
	(16)	ND	770
26		$34\mu M(Ki)$	875
27		ND	102
	(2)	ND	87
	(16)	ND	90
28		$50\mu M(K_i)$	116
29		ND	45
30		$55\mu M(K_i)$	163
31		ND	39
32		ND	98
33		86(10)	361
34		ND	13,400
	(2)	ND	940
	(16)	ND	2,065
35		ND	22,500
	(2)	ND	1,600
	(16)	ND	3,480
36		ND	2,000
	(2)	ND	400
	(16)	ND	750
37		ND	12,400

	(2)	ND	2,500
	(16)	ND	4,000
38		ND	18,200
39		ND	2,330
40		ND	12,100
41		ND	2,350
42		ND	15,000
43		ND	2,200
44		ND	12,300
45		ND	2,300
46		ND	36,800
47		ND	6,500
48		ND	14,050
49		ND	1,910
50		ND	14,000
51		ND	43,900
52		ND	31,100
53		ND	242
54		55(10)	ND
55		20(10)	ND
56		ND	15,400
57		ND	13,500
58		ND	24,300
59		2.8	108,000

In the above table, all data is for RVP serotype-14 unless otherwise noted in parentheses. All strains of human rhinovirus (HRV) were purchased from American Type Culture Collection (ATCC), except for serotype 14, which was produced from the infectious cDNA clone constructed and supplied to us by Dr. Roland Rueckert at the

Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. The column designated INHIB represents the percent inhibition, with the concentration of the compound in μM indicated in parentheses, unless K_i was assigned as designated by (K_i), at 10 minute preincubation with 50 nM RVP prior to addition of substrate was used. The data in the column designated $k_{obs/I}$ was measured from progress curves in enzyme start experiments. The designation NI indicates that no inhibition was obtained when 10 μM of a compound was used. The designation ND indicates that a value was not determined for that compound.

Antirhinoviral HI-HeLa Cell Culture Assay

In the Cell Protection Assay, the ability of compounds to protect cells against HRV infection was measured by the XTT dye reduction method. This method is described in O.S. Weislow, R. Kiser, D.L. Fine, J. Bader, R.H. Shoemaker, and M.R. Boyd, *J. Natl. Cancer Inst.* 1989, 81, 577-586, which document is entirely incorporated herein by reference.

HI-HeLa cells were infected with HRV-14 (unless otherwise noted) at a multiplicity of infection (m.o.i.) of 0.13 (virus particles/cell) or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8 x 10^5 cells per mL and incubated with appropriate concentrations of compounds of formulas I and II. Two days later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free

mock-infected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in compound-treated, mock-infected cells to 50% of that produced in compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

All strains of human rhinovims (HRV) for use in this assay were purchased from American Type Culture Collection (ATCC), except for HRV serotype-14, which was produced from the infectious cDNA clone, constructed and supplied to us by Dr. Roland Rueckert at the Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. HRV stocks were propagated, and antiviral assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium, available from Life Technologies, with 10% fetal bovine serum.

The compounds were tested against control compounds WIN 51711, WIN 52084, and WIN 54954, all obtained from Sterling-Winthrop Pharmaceuticals, and control compound Pirodavir, obtained from Janssen Pharmaceuticals. Antiviral data obtained for the test compounds are shown in Table 2 where all data are for HRV serotype-14 unless otherwise noted in parentheses.

TABLE 2

Compound #	EC_{50}(μM)	CC_{50}(μM)	TI
1	20	251	13
2	1.0	56	56
3	0.18	41.7	232
4	0.23	200	870

5	0.24	51.4	214
6	2.8	151.4	54
7	1.3	47.9	37
8	10	>320	>32
9	0.25	56.2	225
10	1.8	56.2	31
11	0.53	>320	>603
12	4.2	>320	>76
13	0.12	17.8	148
14	0.32	15.8	49
15	0.26	50.1	192
16	1.7	32	19
17	0.5	53	106
18	5.0	126	25
19	50	>320	>6
20	5.4	56	10.3
21	22	>320	>15
22	177.8	>320	>2
23	10	224	22
24	10	>100	>10
25	14	>320	>23
26	56	>320	>5
27	>320	>320	
28	6.9	125	18
29	46	251	5
30	7.2	177	25
31	56	>320	>6
32	158	>320	>2

33	>320	>320	
34	0.32	>100	>312
35	0.19	>100	>526
36	11.2	>100	>9
37	8.9	>100	>11
38	0.36	>100	>278
39	1.6	180	113
40	0.32	45	141
41	2.0	18	9
42	0.45	50.1	111
43	3.5	56.2	16
44	0.54	56.2	104
45	1.78	56.2	32
46	0.54	18	33
47	1.3	18	14
48	0.5	>10	>20
49	0.1	71	710
50	3.2	>100	>31
51	12.6	>100	>8
52	32	>100	>3
53	4.5	>100	>22
54	17.8	>100	>6
55	50	>100	>2
56	1.6	20	13
57	0.56	50	89
58	0.56	63	113
59	0.14	>100	>714
59 (HRV 1A)	0.40	>100	>250

59 (HRV 10)	0.40	>100	>250
WIN 51711	0.78	>60	>77
WIN 52084	0.07	>10	>143
WIN 54954	2.13	>63	>30
Pirodavir	0.03	>10	>300

Anticoxsackieviral Hi HeLa Cell Culture Assay

The ability of compounds to protect cells against CVA-21 or CVB-3 infection was measured by the XTT dye reduction method. Briefly, HI-HeLa cells were infected with CVA-21 or CVB-3 at a multiplicity of infection (m.o.i.) of 0.05 (CVA-21) and 0.08 (CVB-3) or mock-infected with medium only. Infected or uninfected cells were resuspended at 4 x 10^4 cells per mL and incubated with appropriate concentrations of drug. One day later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of drug that increased the percentage of formazan production in drug-treated, virus-infected cells to 50% of that produced by drug-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of drug that decreased the percentage of formazan produced in drug-treated, uninfected cells to 50% of that produced in drug-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

The Coxsackie strains A-21 (CVA-21) and B-3 (CVB-3) were purchased from American Type Culture Collection (ATCC). Virus stocks were propagated and antiviral

assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium with 10% fetal bovine serum.

Table 3. Antiviral efficacy of compounds against CVB-3 infection of Hi-HeLa cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	2.0	56	28
WIN 54954	>100	>100	
Pirodavir	>100	>100	

Table 4. Antiviral efficacy of compounds against CVA-21 infection of Hi-HeLa cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	3.3	56	17
4	1.8	200	111
WIN 54954	>100	>100	
Pirodavir	>100	>100	

Echovirus-11 and Enterovirus-70 MRC5 Cell Culture Assay

The Echovirus strain 11 (ECHO-11) and Enterovirus strain 70 (ENT-70) were purchased from American Type Culture Collection (ATCC). Virus stocks were propagated and antiviral assays were performed in MRC5 cells (ATCC). Cells were grown in Minimal Essential Medium with 10% fetal bovine serum.

The ability of compounds to protect cells against ECHO-11 or ENT-70 infection was measured by the XTT dye reduction method. Briefly, MRC5 cells were infected

with ECHO-11 or ENT-70 at a multiplicity of infection (m.o.i.) of 0.0013 (ECHO-11) and 0.0017 (ENT-70) or mock-infected with medium only. Infected or uninfected cells were resuspended at 2 x 10^4 cells per mL and incubated with appropriate concentrations of drug. One day later, XTT /PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of drug that increased the percentage of formazan production in drug-treated, virus-infected cells to 50% of that produced by drug-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of drug that decreased the percentage of formazan produced in drug-treated, uninfected cells to 50% of that produced in drug-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

Table 5. Antiviral efficacy of compounds against ECHO-11 infection of MRC5 cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	3.1	56	18
4	3.2	200	62.5
WIN 54954	>100	>100	
Pirodavir	>100	>100	

Table 6. Antiviral efficacy of compounds against ENT-70 infection of MRC5 cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	0.6	56	93
4	0.3	200	667

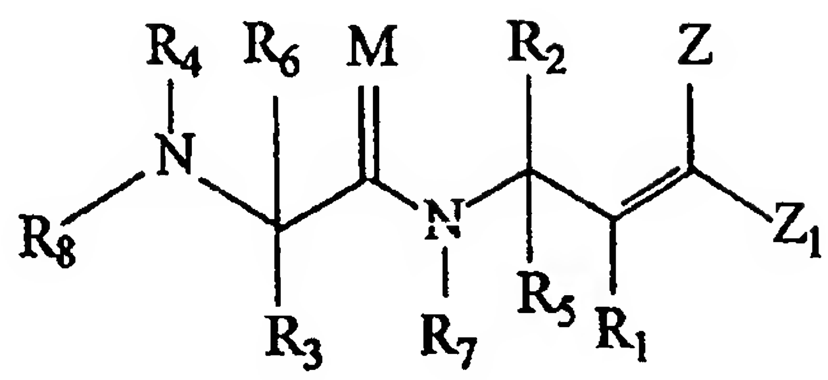
WIN 54954	> 100	> 100	
Pirodavir	> 100	> 100	

In describing the invention, the inventors have set forth certain theories and mechanisms in an effort to disclose how or why the invention works in the manner in which it works. These theories and mechanisms are set forth for informational purposes only. Applicants are not to be bound by any specific chemical or physical mechanisms or theories of operation.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof. Thus, it is intended that the present invention cover the modifications and variations, provided they come within the scope of the appended claims and their equivalents.

WE CLAIM:

1. A compound of formula (I):



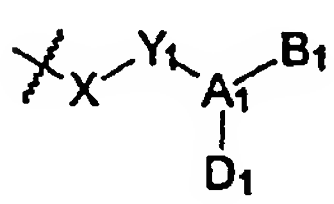
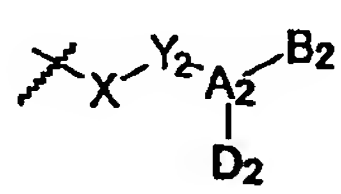
(I),

wherein:

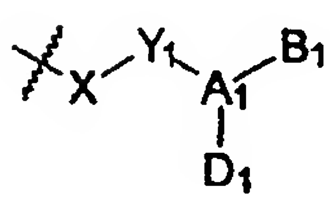
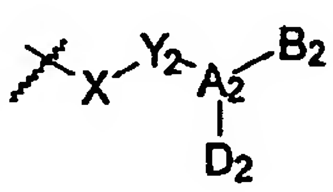
M is O or S;

R_1 is H, F, an alkyl group, OH, SH, or an O-alkyl group;

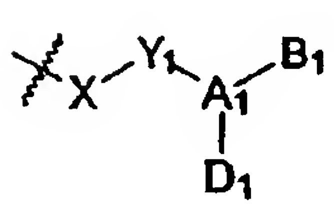
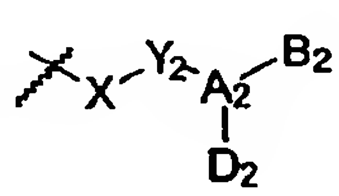
R_2 and R_5 are independently selected from H,

 ,  ,

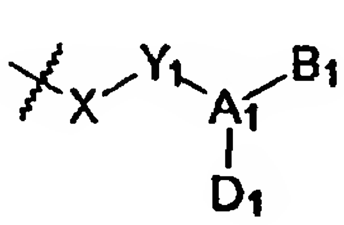
or an alkyl group, wherein said alkyl group is different from

 and  ,

with the proviso that at least one of R_2 or R_5 must be

 or  ,

and wherein, when R_2 or R_5 is

 ,

X is =CH or =CF and Y_1 is =CH or =CF,

or X and Y_1 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y is $-CH-$, $-CF-$, or $-C(alkyl)-$,

where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_1 is $-O-$, $-S-$, $-NR_{12}-$, $-C(R_{13})(R_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR_{13}R_{14})-$,

wherein R_{12} is H or alkyl, and R_{13} and R_{14} independently are H, F, or an alkyl group, or, together with the atoms to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

A_1 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

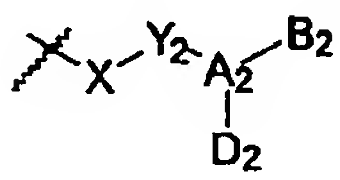
D_1 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and B_1 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N;

and further wherein, when R_2 or R_5 is



,

X is = CH or = CF and Y_2 is =C, =CH or = CF,

or X and Y_2 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_2 is $-CH-$, $-CF-$, or $-C(alkyl)-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_2 is $-O-$, $-S-$, $-N(R'_{12})-$, $-C(R'_{13})(R'_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR'_{13}R'_{14})-$,

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR'_{13}$, $-NR'_{13}R'_{14}$, $-C(O)-R'_{13}$, $-SO_2R'_{13}$, or $-C(S)R'_{13}$, and R'_{13} and R'_{14}, independently are H, F, or an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl

group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

A_2 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), P-OR_{15}, or P-$NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and further wherein any combination of Y_2, A_2, B_2, and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

R_3 and R_6 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{17}$, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or, R_3 and R_6, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group; R_4 is any suitable organic moiety, or R_4 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

R_7 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or R_7, together with R_3 or R_6 and the atoms to which they are attached, forms a heterocycloalkyl group;

R_8 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-NR_{29}R_{30}$, $-OR_{29}$, or $-C(O)R_{29}$,

wherein R_{29} and R_{30} each independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

or R_8, together with R_4 and the nitrogen atom to which they are attached, forms a heterocycloalkyl group or a heteroaryl group, or R_8 and R_3 or R_6, together with the atoms to which they are attached, forms a heterocycloalkyl group;

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

or Z_1, as defined above, together with R_1, as defined above, and the atoms to which Z_1 and R_1 are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z_1, both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

with the proviso that when R_7 is H, R_8 is a moiety other than H;

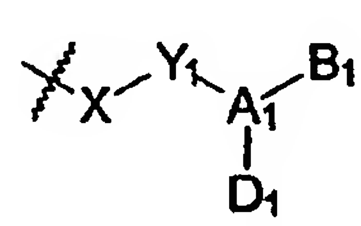
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof;

and wherein said compound, pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof has antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

2. A compound of claim 1, wherein R_1 is H or F, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

3. A compound of claim 1, wherein at least one of R_4 and R_8 is an acyl group or a sulfonyl group, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

4. A compound of claim 1, wherein at least one of R_2 or R_5 is



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or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

5. A compound according to claim 4, wherein D_1 is $-OR_{25}$, $=O$, $=S$, $\equiv N$, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

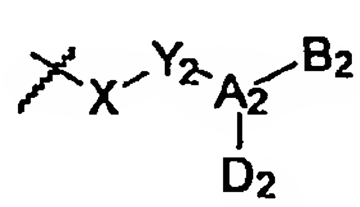
6. A compound according to claim 5, wherein D_1 is $=O$; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

7. A compound according to claim 4, wherein A_1 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

8. A compound according to claim 7, wherein A_1 is C; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

9. A compound according to claim 4, wherein B_1 is $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

10. A compound according to claim 1, wherein at least one of R_2 or R_5 is



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or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

11. A compound according to claim 10, wherein D_2 is $-OR_{25}$, $=O$, $=S$, $\equiv N$, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or,

together with the atom(s) to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

12. A compound according to claim 11, wherein D_2 is $=O$; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

13. A compound according to claim 10, wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

14. A compound according to claim 13, wherein A_2 is C; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

15. A compound according to claim 10, wherein B_2 is $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

16. A compound according to claim 1, wherein A_1 is C, CH, S, or S(O) or wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

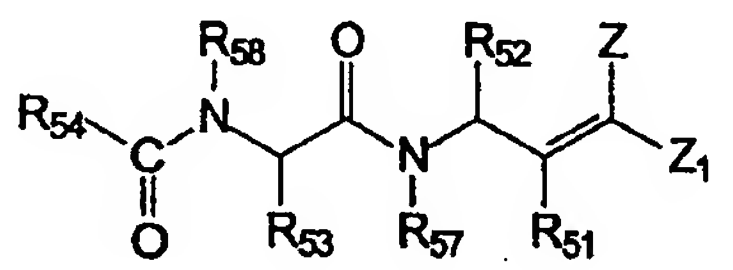
17. A compound according to claim 1, wherein Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$ $-SO(NR_{21})(OR_{22})$, $SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$;

wherein R_{21}, R_{22}, and R_{23} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, and R_{23}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

18. A compound according to claim 1, wherein M is O, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

19. A compound having the formula II:

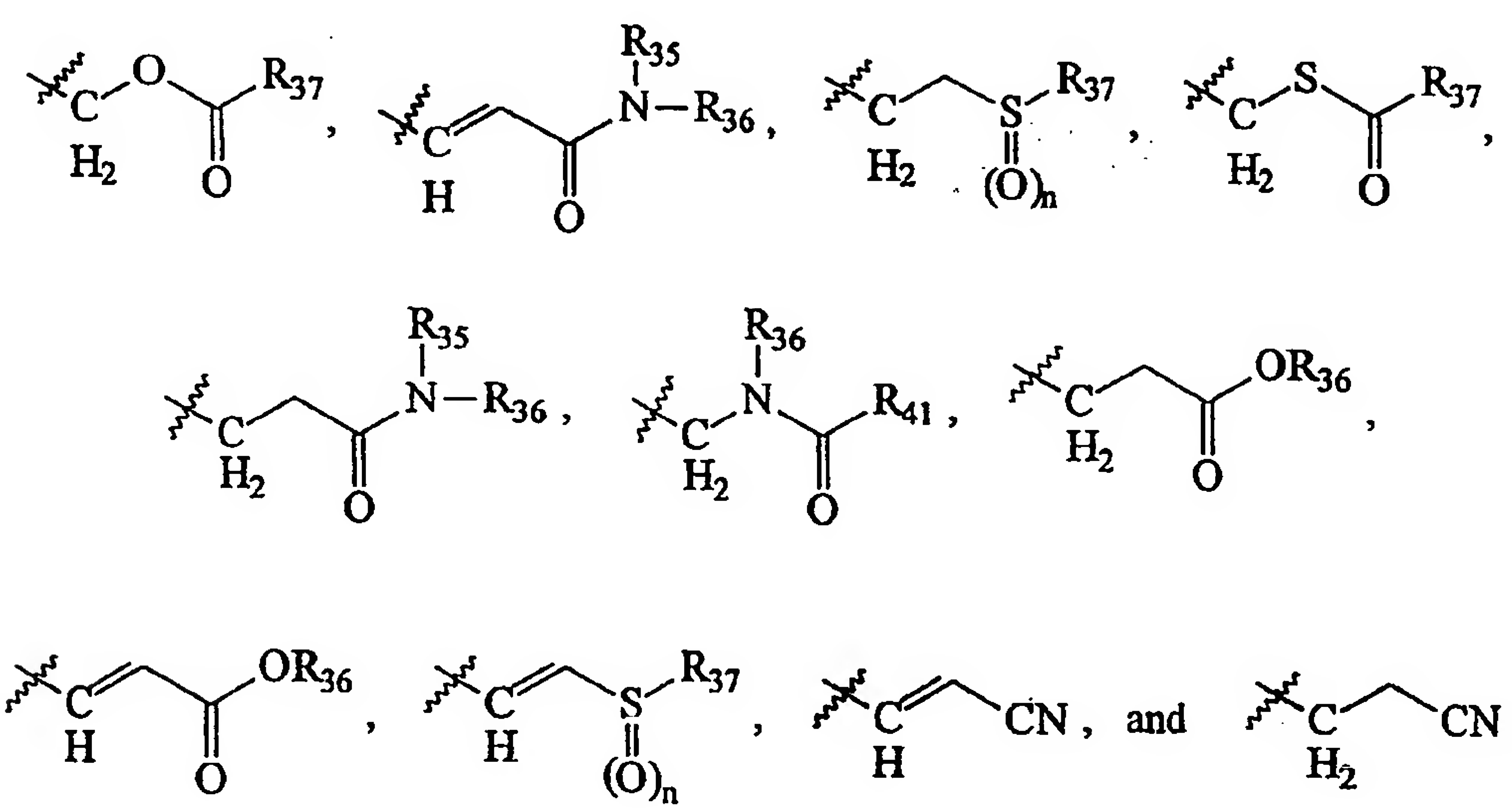


(II),

wherein:

R_{51} is H, F, or an alkyl group;

R_{52} is selected from one of the following moieties:



wherein:

R_{35} is H, an alkyl group, an aryl group, $-OR_{38}$, or $-NR_{38}R_{39}$,

wherein R_{38} and R_{39} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

R_{36} is H or an alkyl group,

or R_{35} and R_{36}, together with the nitrogen atom to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$, wherein R_{38} and R_{39} are as defined above;

R_{41} is H, an alkyl group, an aryl group, $-OR_{38}$, $-SR_{39}$, $-NR_{38}R_{39}$, $-NR_{40}NR_{38}R_{39}$, or $-NR_{38}OR_{39}$, or R_{41} and R_{36}, together with the atoms to which they are attached, form a heterocycloalkyl group, and

wherein R_{38} and R_{39} are as defined above and R_{40} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

n is 0, 1 or 2;

R_{53} is H or an alkyl group;

R_{54} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl group, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group;

or R_{54}, together with R_{58} and the nitrogen atom to which they are attached, forms a heterocycloalkyl group or a heteroaryl group;

R_{57} is H or an alkyl group;

R_{58} is H, an alkyl group, a cycloalkyl group, $-OR_{70}$, or $-NR_{70}R_{71}$, wherein R_{70} and R_{71} are independently H or an alkyl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

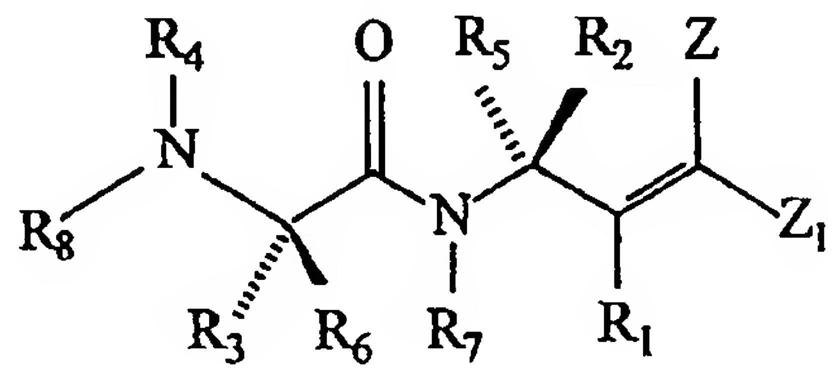
wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or wherein Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group;

with the proviso that when R_{57} is H, R_{58} is a moiety other than H;

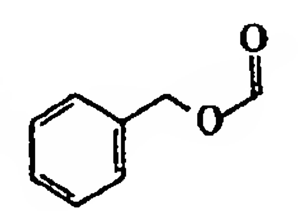
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

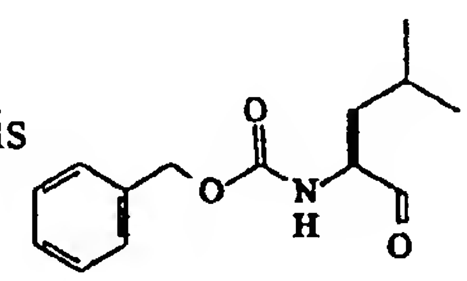
20. A compound according to claim 1, having the formula Ia:

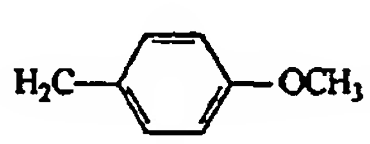
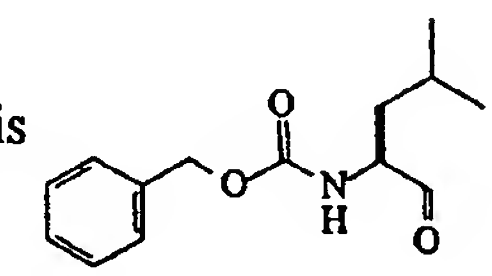


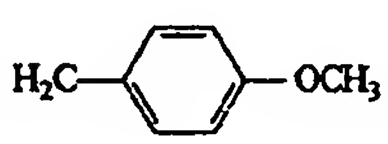
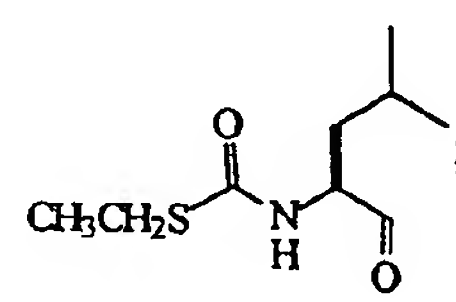
(Ia),

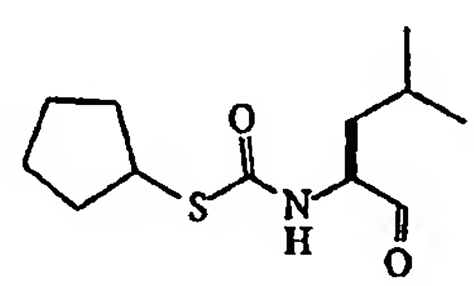
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

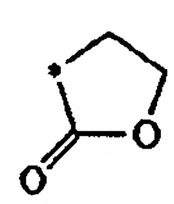
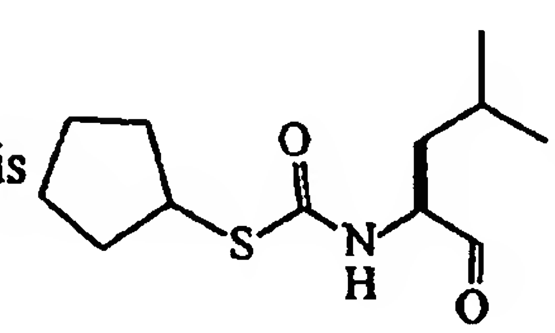
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

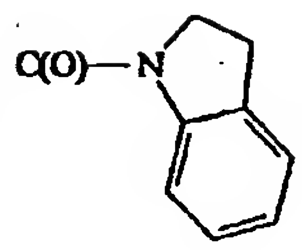
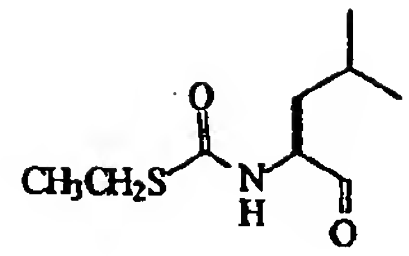
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

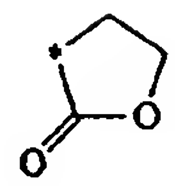
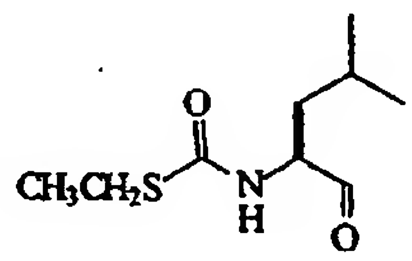
Z is H; Z_1 is $CO_2CH_2CH_3$, R_3 is  , and R_8 is  ;

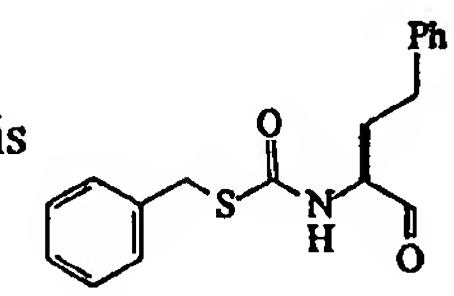
R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

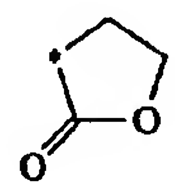
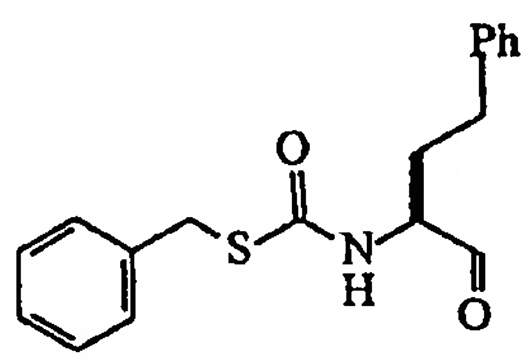
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

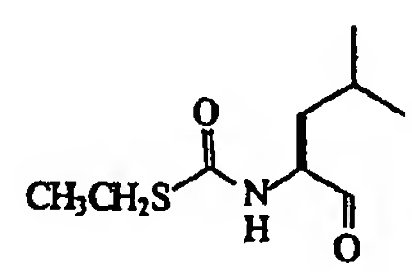
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O is cis to the R_1 group), and R_8 is  ;

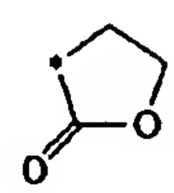
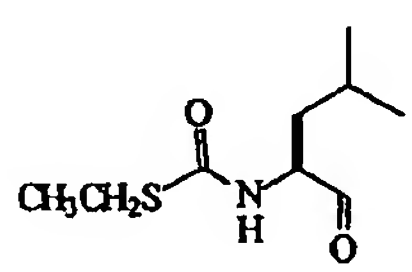
R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is ;

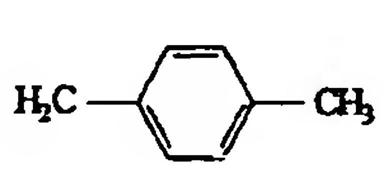
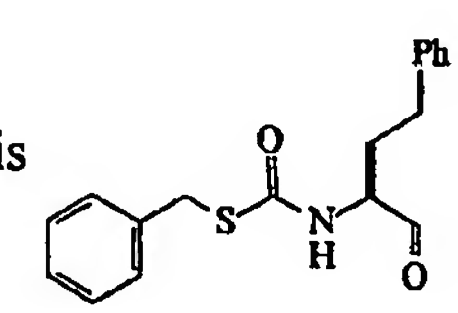
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is ;

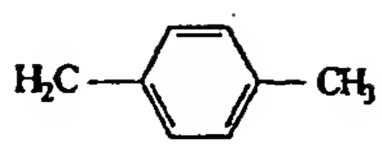
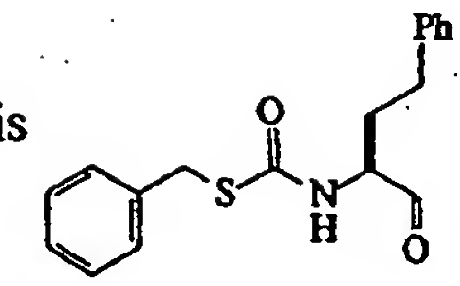
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

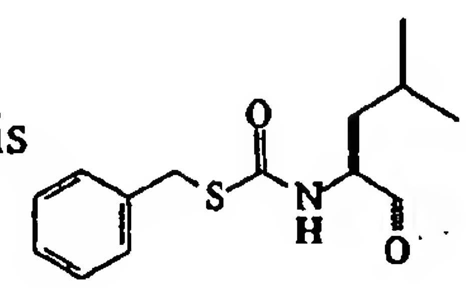
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is ;

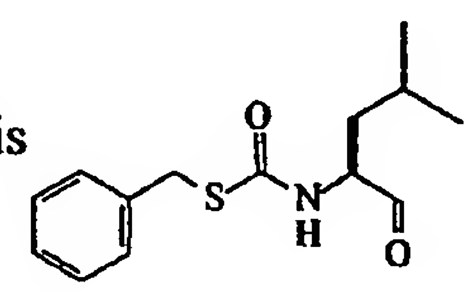
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

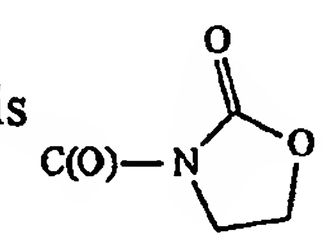
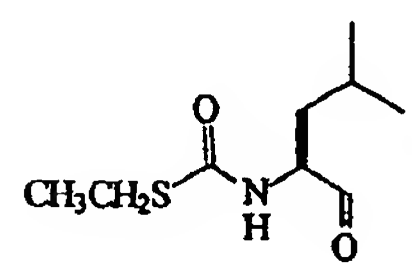
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is ;

R_3 is , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

R_3 is  , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

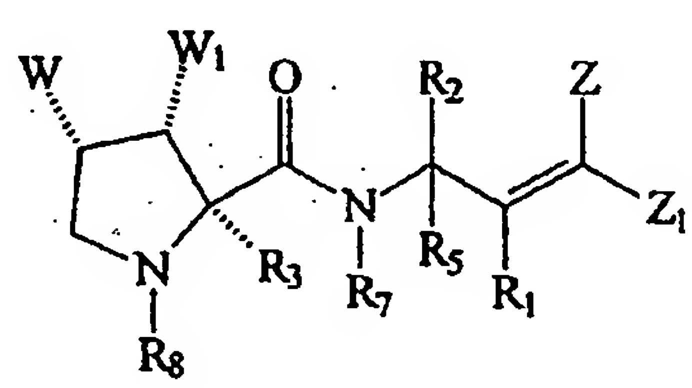
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ; and

R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is  ,

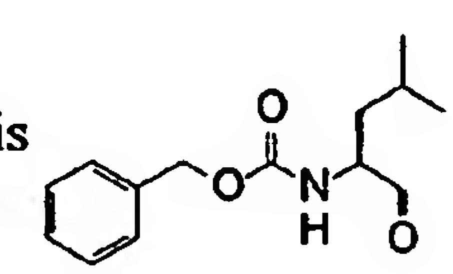
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

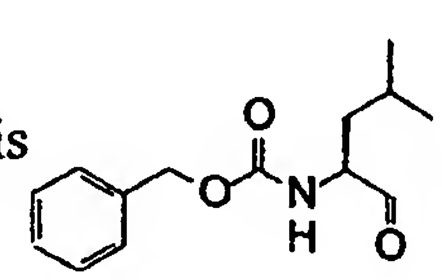
21. A compound according to claim 1, having the formula Ib:

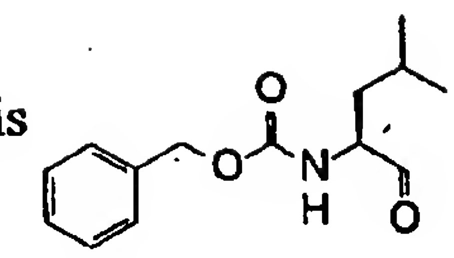


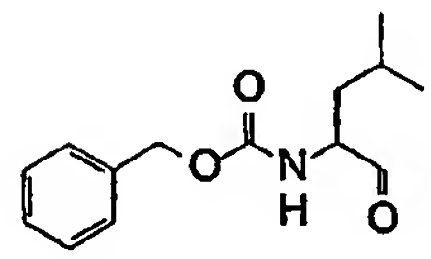
(Ib),

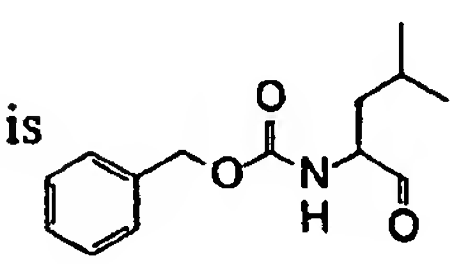
wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, and Z_1, W, W_1, and R_8 are selected from one of the following groups:

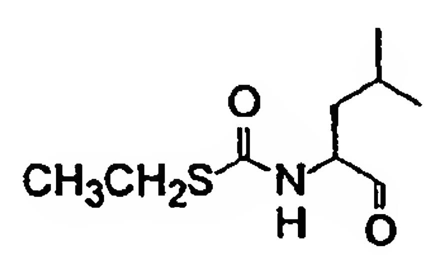
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is Ph, and R_8 is  ;

Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  ;

Z_1 is $CO_2CH_2CH_3$, W is OCH_2Ph, W_1 is H, and R_8 is  ;

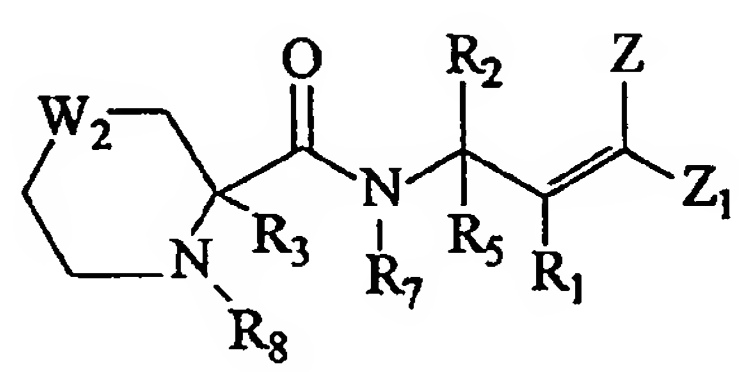
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is CH_3, and R_8 is  ;

Z_1 is $CO_2CH_2CH_3$, W is $OC(CH_3)_3$, W_1 is H, and R_8 is  ; and

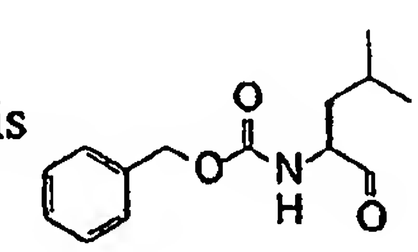
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  ,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

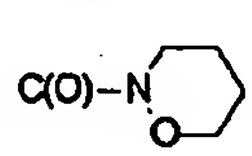
22. A compound according to claim 1, having the formula Ic:



(Ic),

wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_8 is  , and W_2 and Z_1 are selected from one of the following groups:

W_2 is CH_2 and Z_1 is $CO_2CH_2CH_3$;

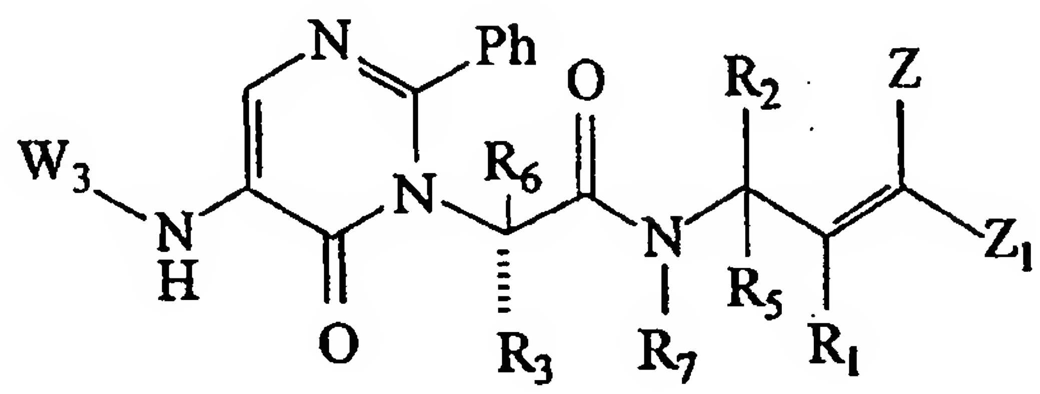
W_2 is CH_2 and Z_1 is  ;

W_2 is NCH_2Ph and Z_1 is $CO_2CH_2CH_3$; and

W_2 is NSO_2Ph and Z_1 is $CO_2CH_2CH_3$,

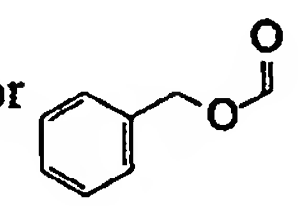
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

23. A compound according to claim 1, having the formula Id:



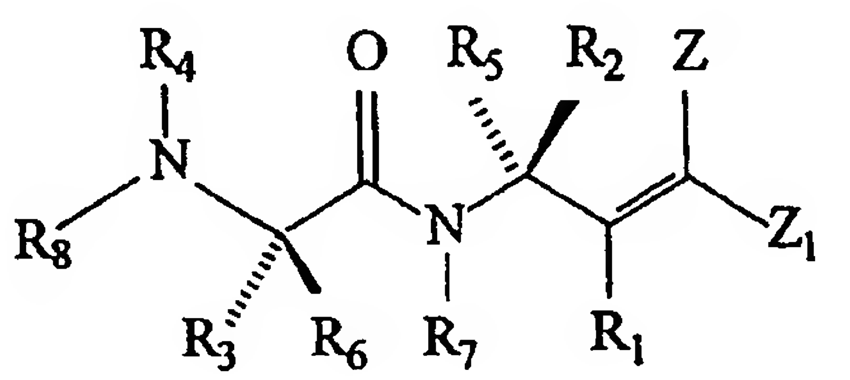
(Id),

wherein R_1, R_3, R_5, R_6, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and

W_3 is H or  ,

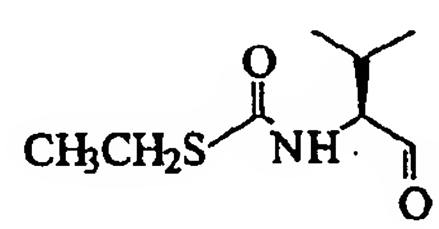
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

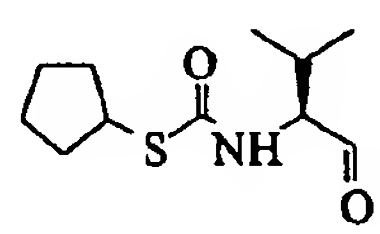
24. A compound according to claim 1, having the formula Ia:

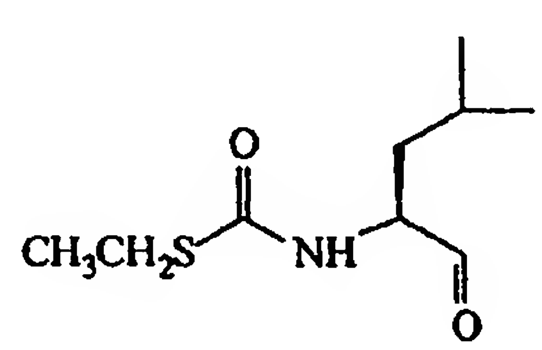


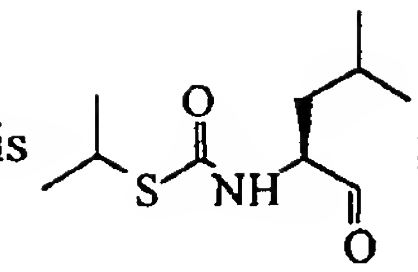
(Ia),

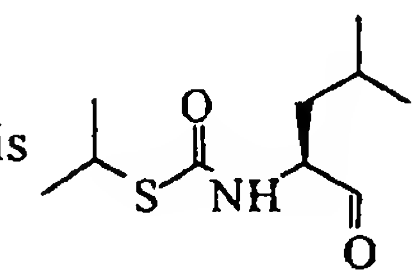
wherein R_1, R_5, R_6, and R_7 are each H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

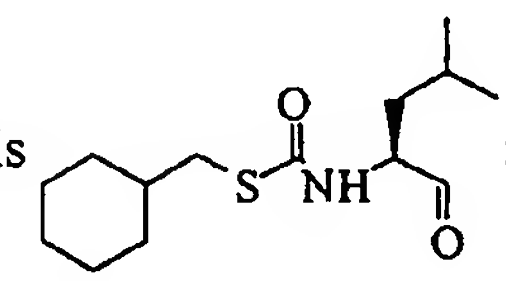
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

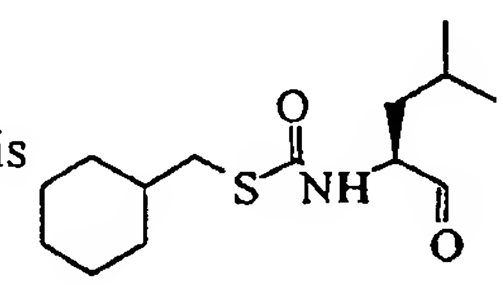
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

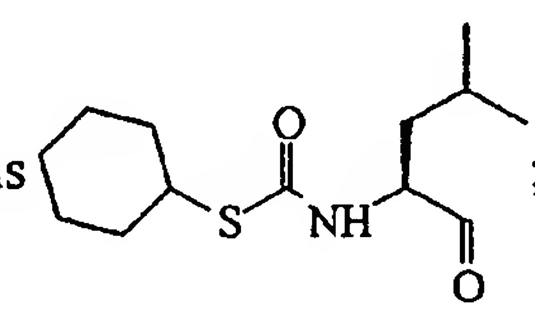
R_3 is CH_2Ph, Z is H, Z_1 is $C(O)N(CH_3)OCH_3$, and R_8 is  ;

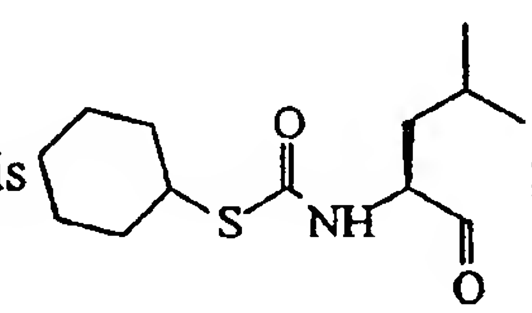
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

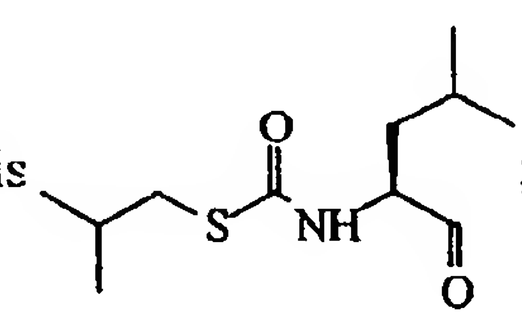
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

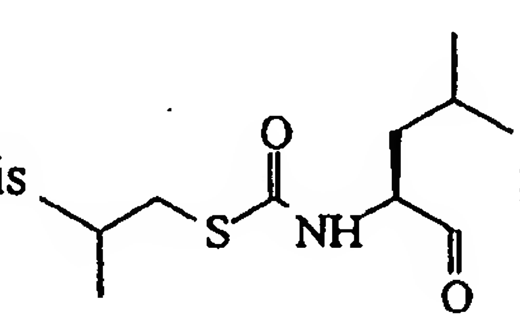
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

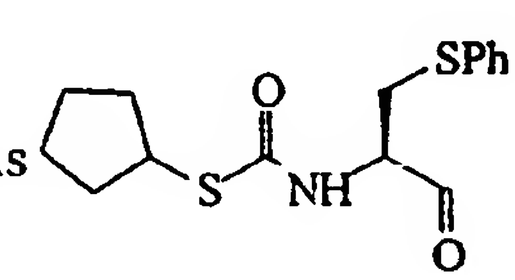
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

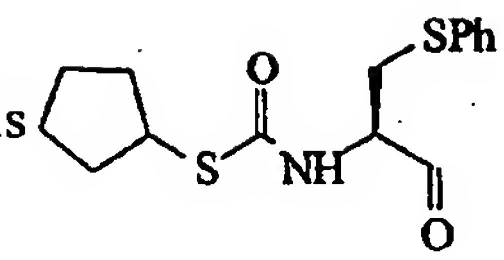
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

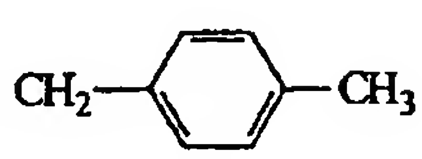
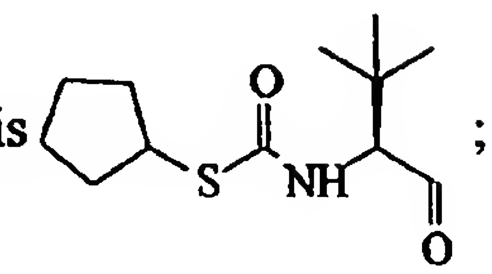
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

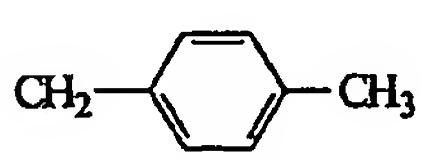
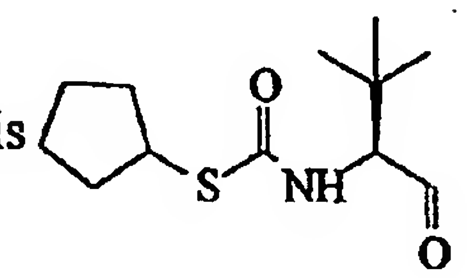
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

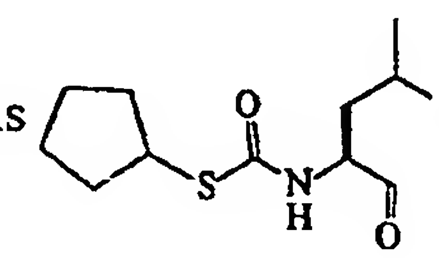
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

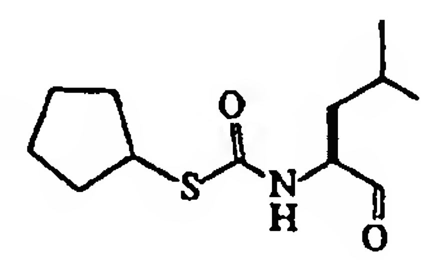
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

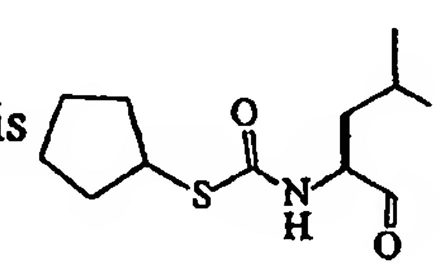
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is  , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

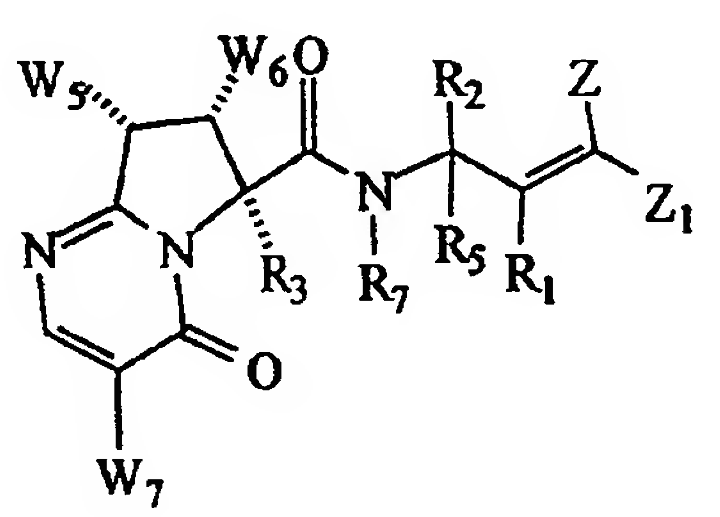
R_3 is CH_2Ph, Z is H, Z_1 is CO_2CH_2Ph, and R_8 is  ;

R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2CH_3$, and R_8 is  ; and

R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2OCH_3$, and R_8 is  ,

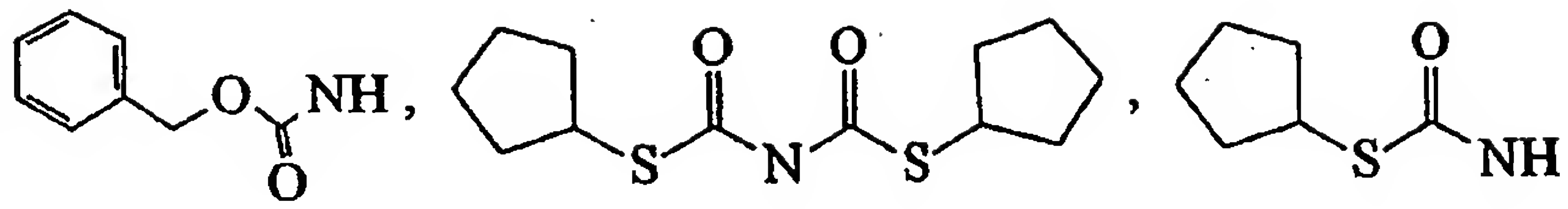
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

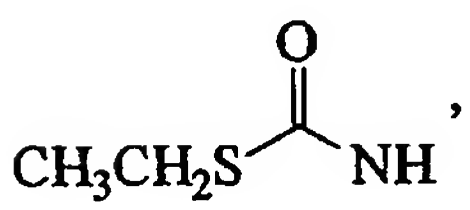
25. A compound according to claim 1, having the formula Ig:



(Ig),

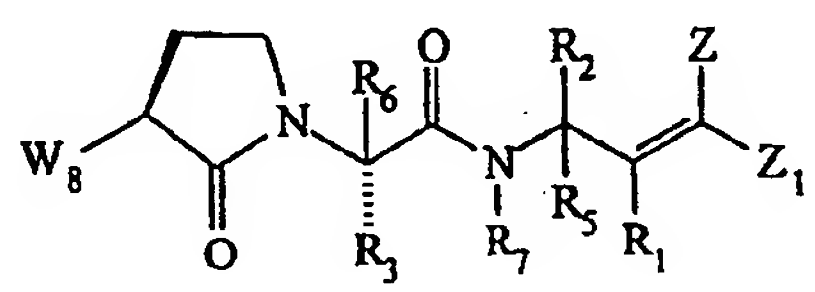
wherein R_1, R_3, R_5, R_7, W_5, W_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_7

is  , or

 ,

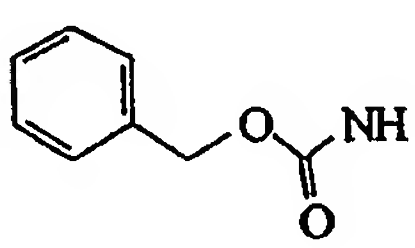
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

26. A compound according to claim 1, having the formula Ih:



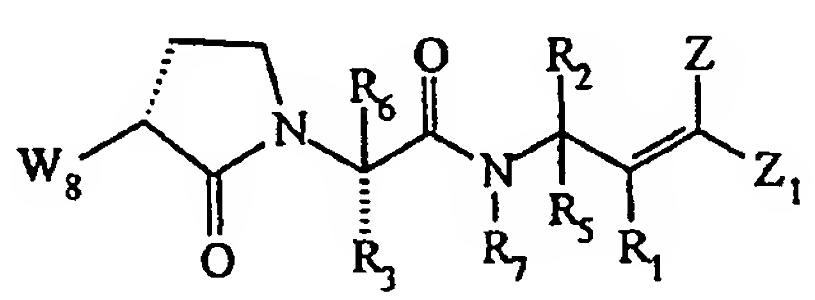
(Ih),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$,

and W_8 is  ,

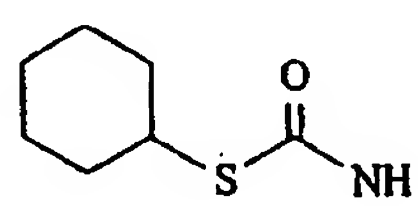
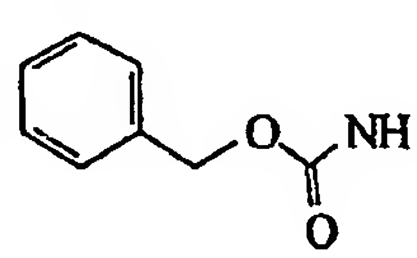
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

27. A compound according to claim 1, having the formula Ij:



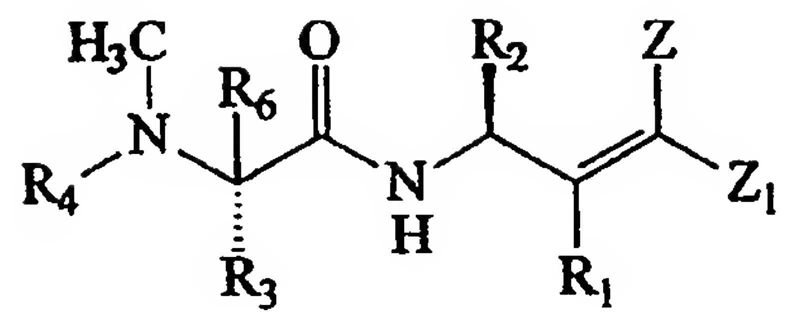
(Ij),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is

$CO_2CH_2CH_3$, and W_8 is  or  ,

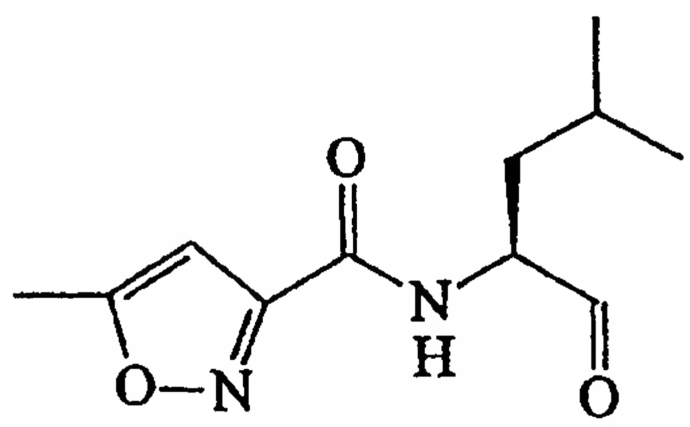
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

28. A compound according to claim 1, having the following formula X:

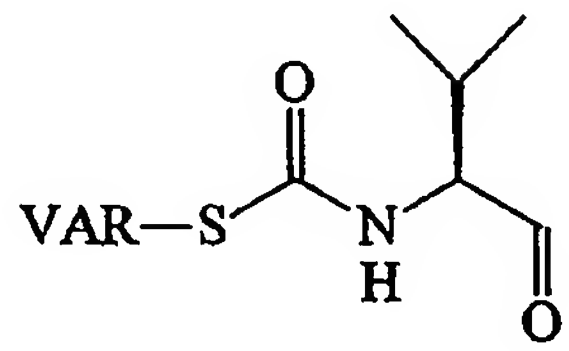


(X),

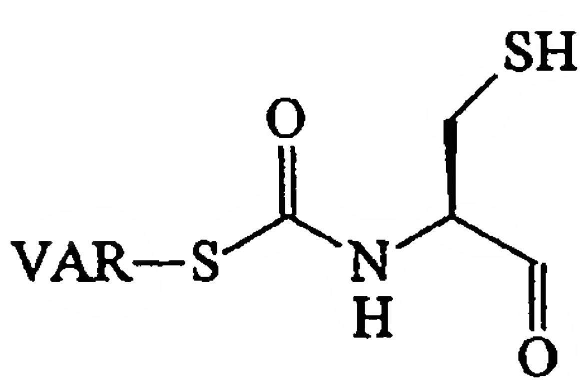
wherein R_1, R_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z_1 is $CO_2CH_2CH_3$, and R_4 is selected from one of the following:



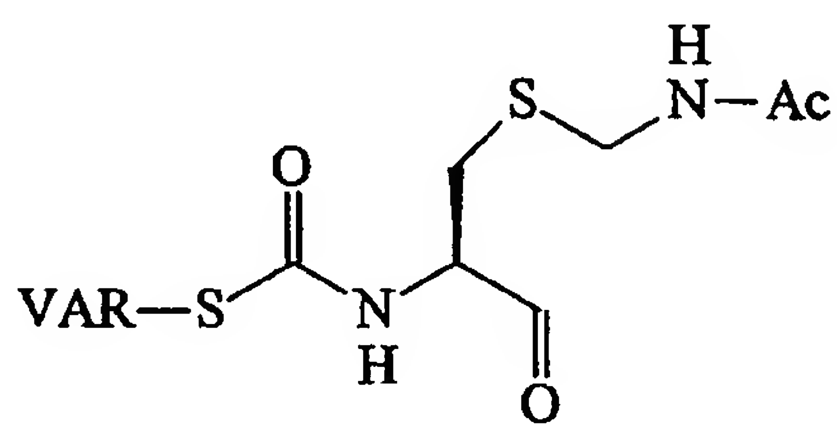
;



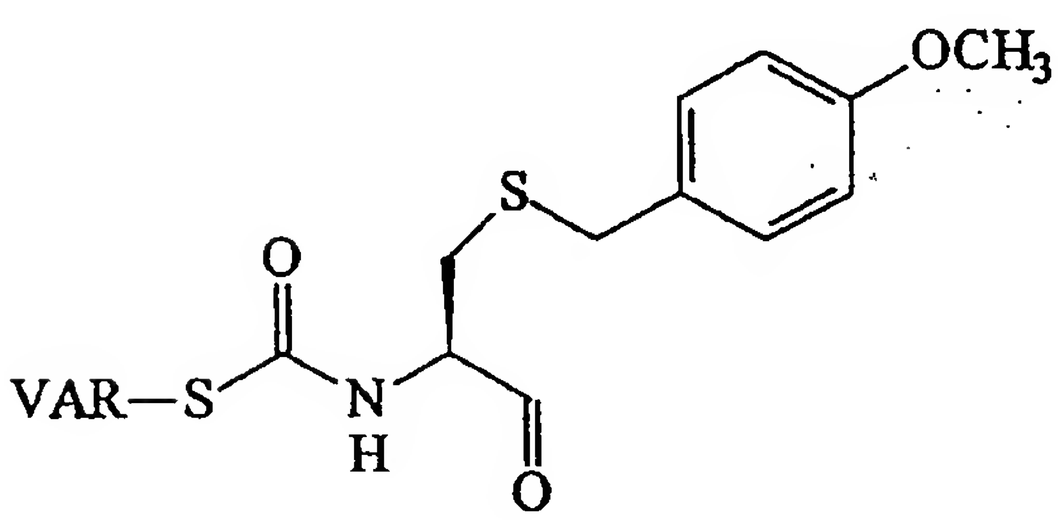
;



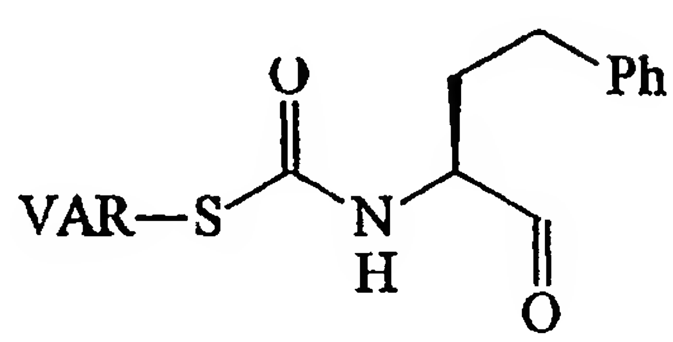
;



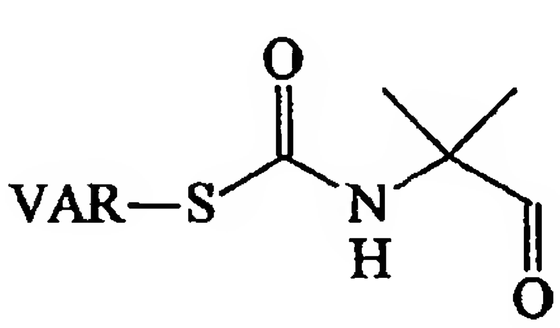
;



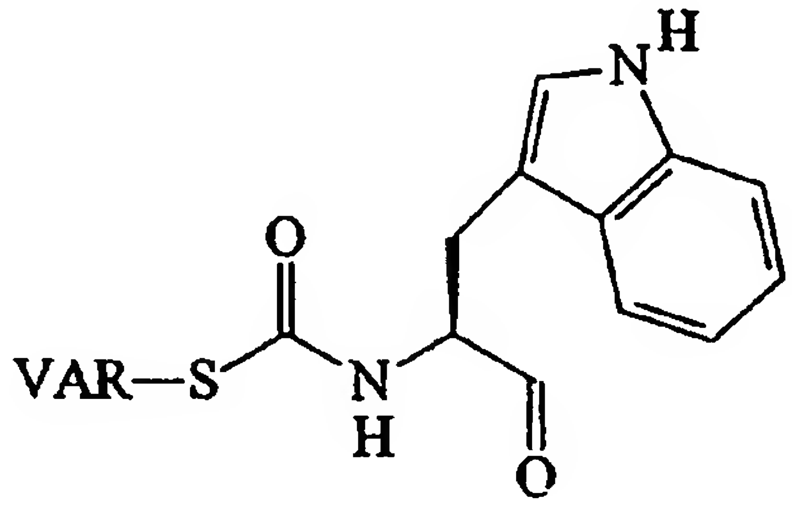
;



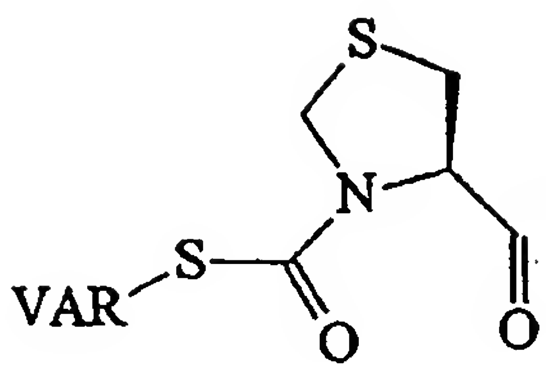
;

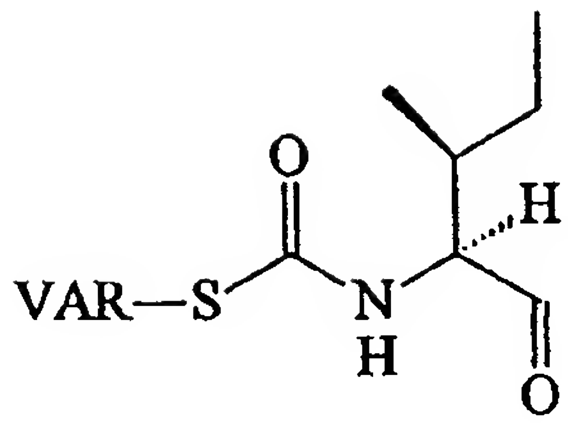


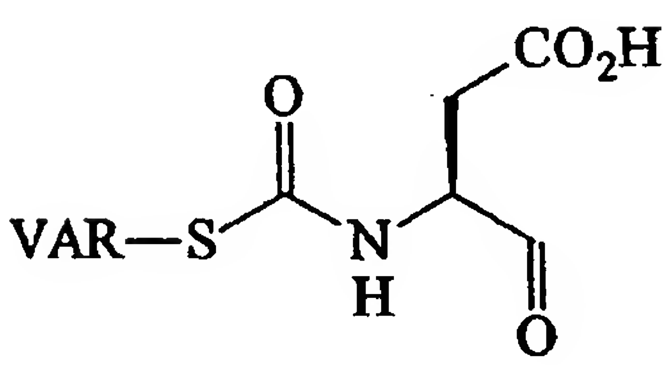
;



;


;


;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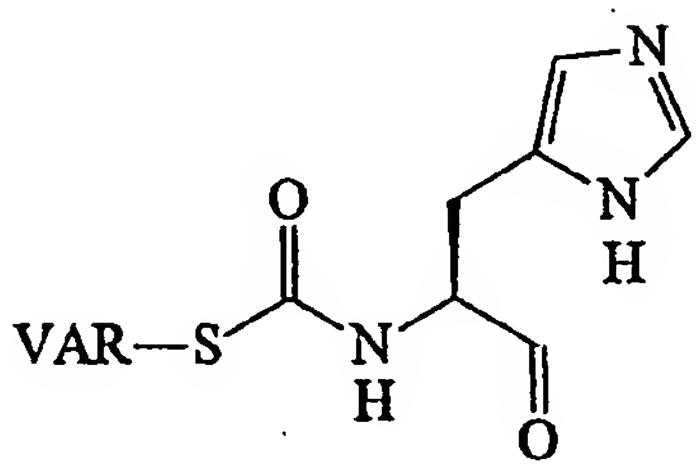
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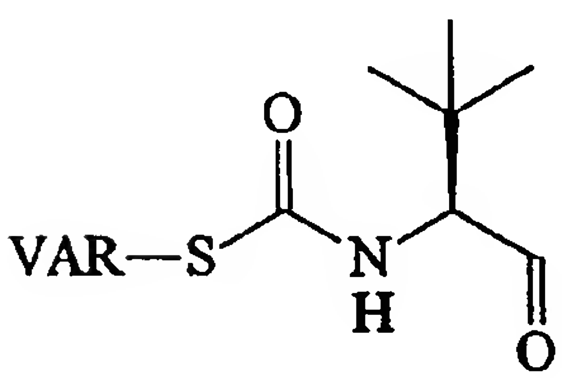
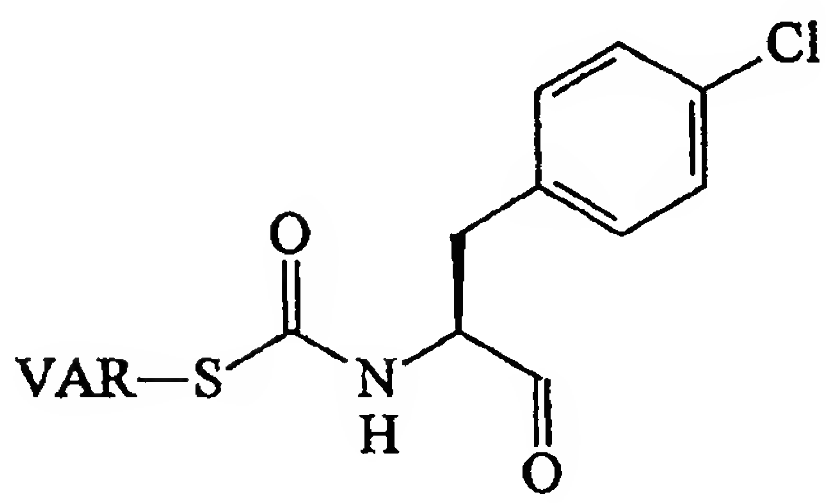
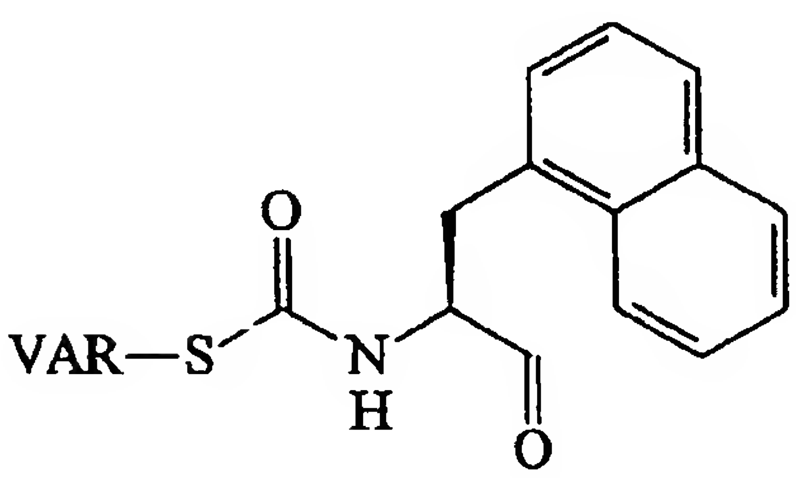

;


;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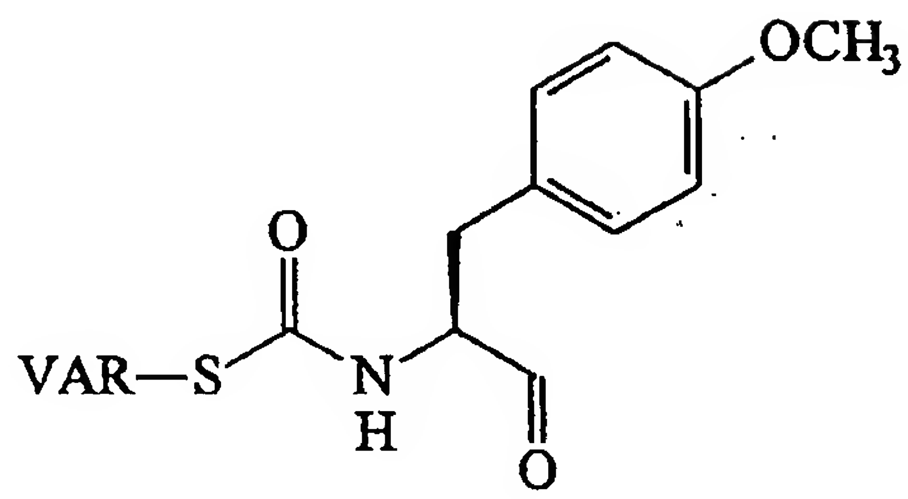
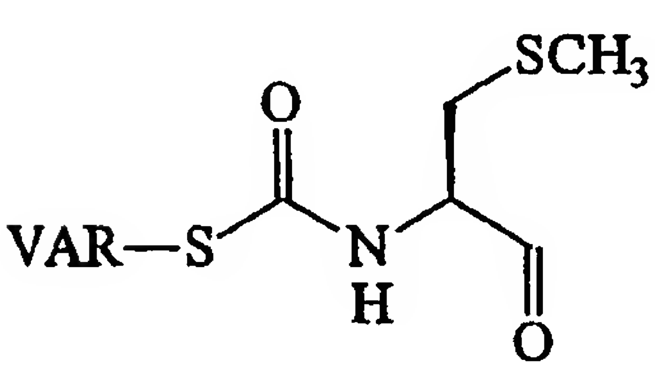
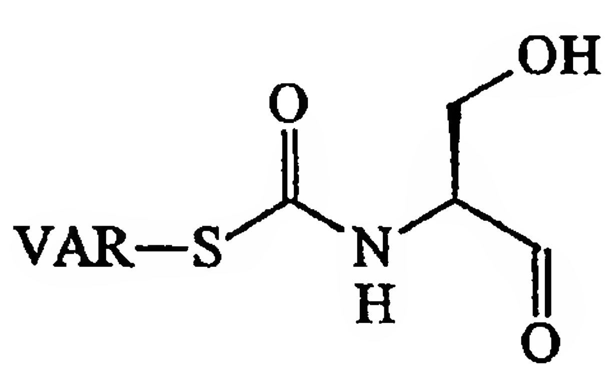

;


;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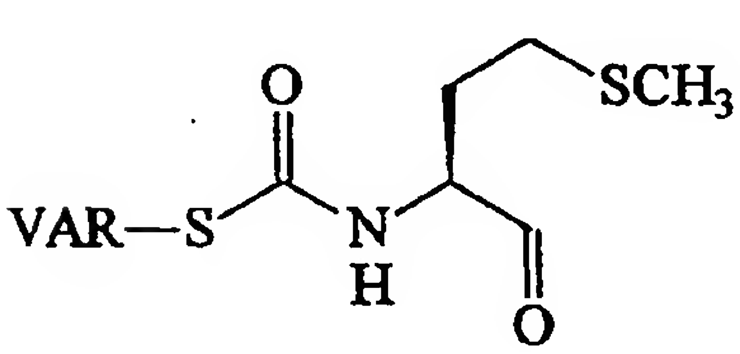
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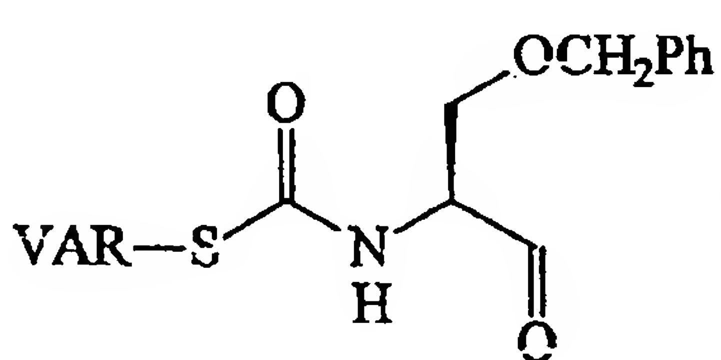
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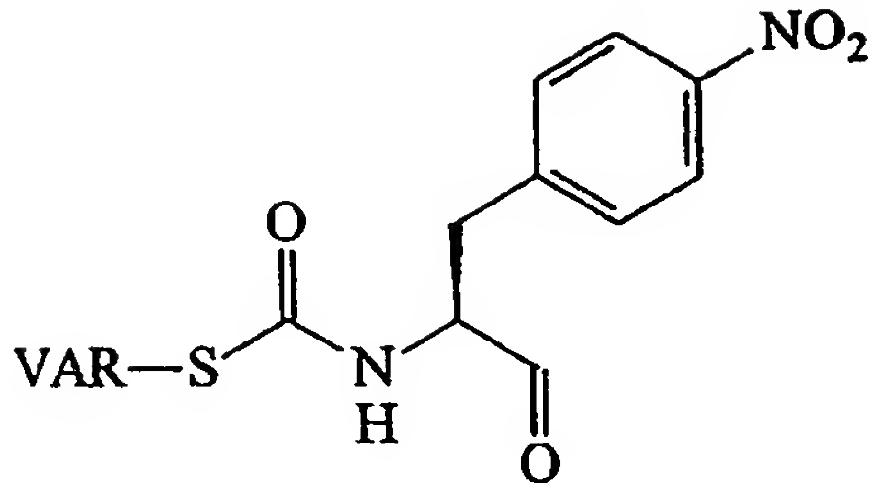
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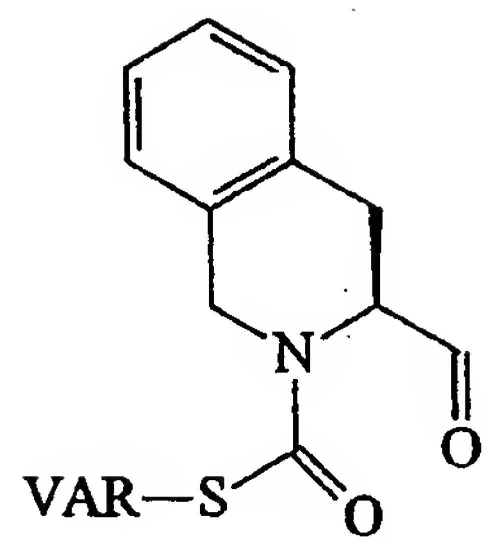
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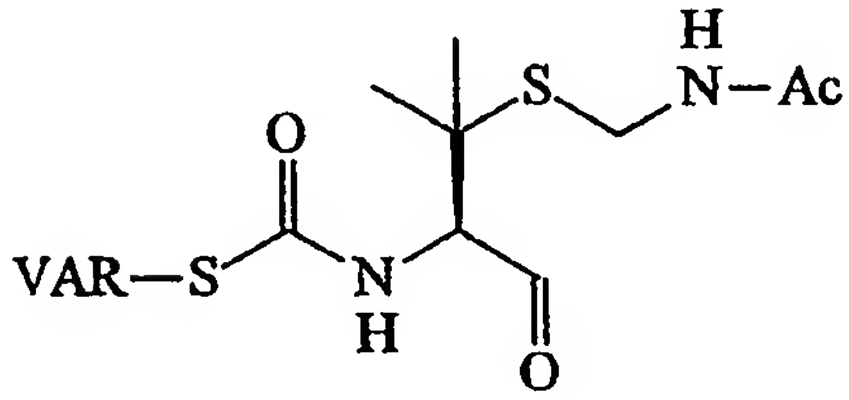
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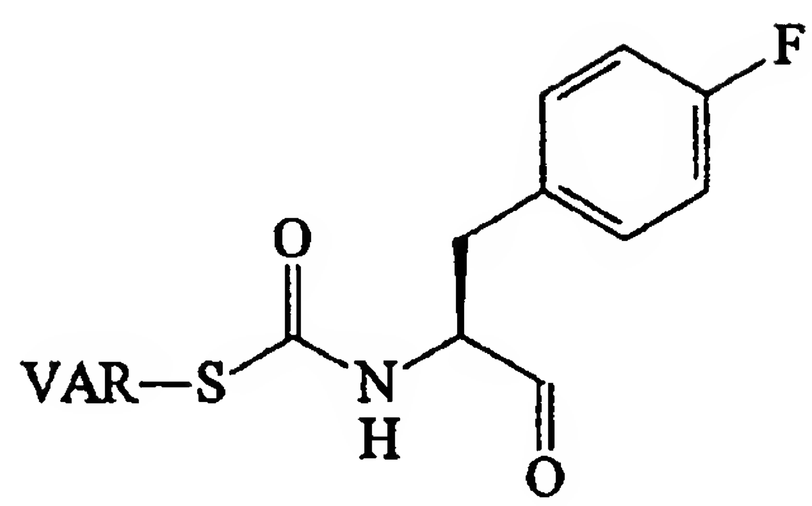
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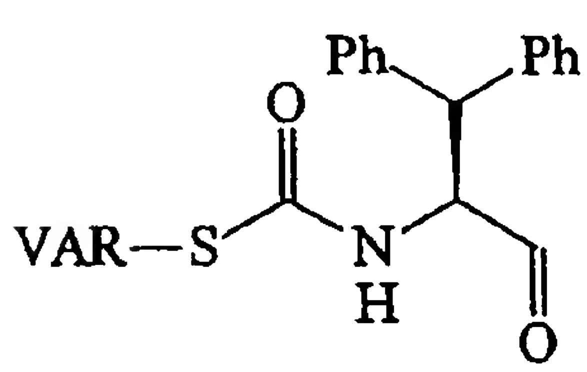
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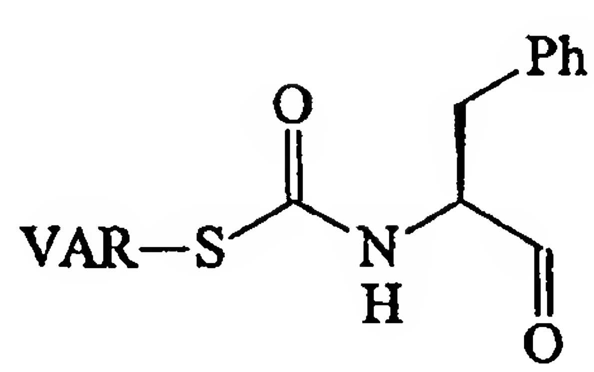
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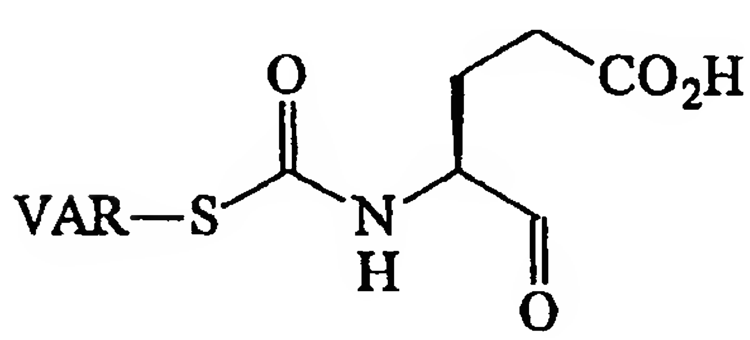
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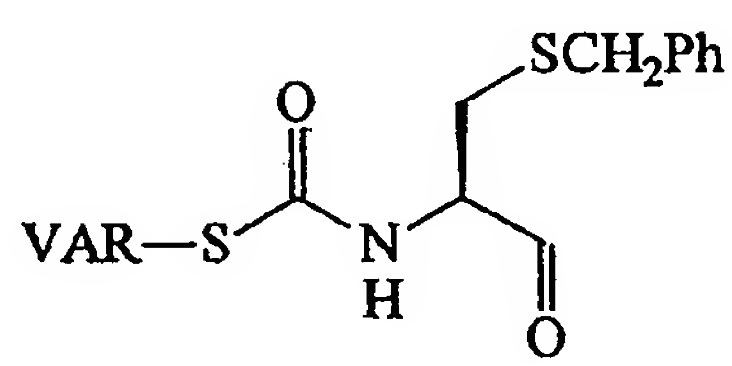
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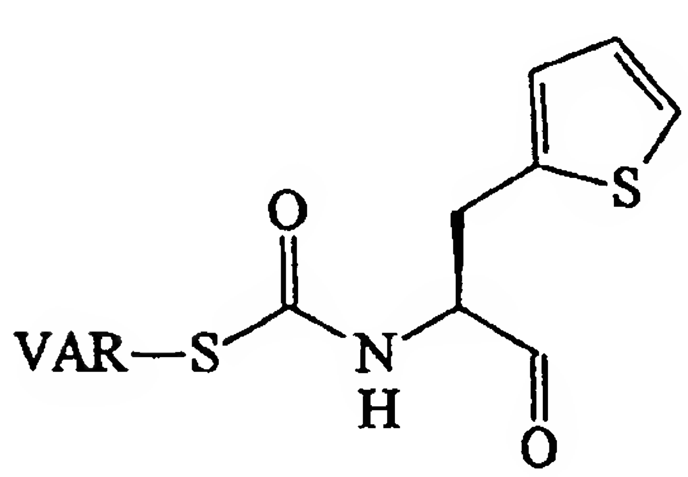
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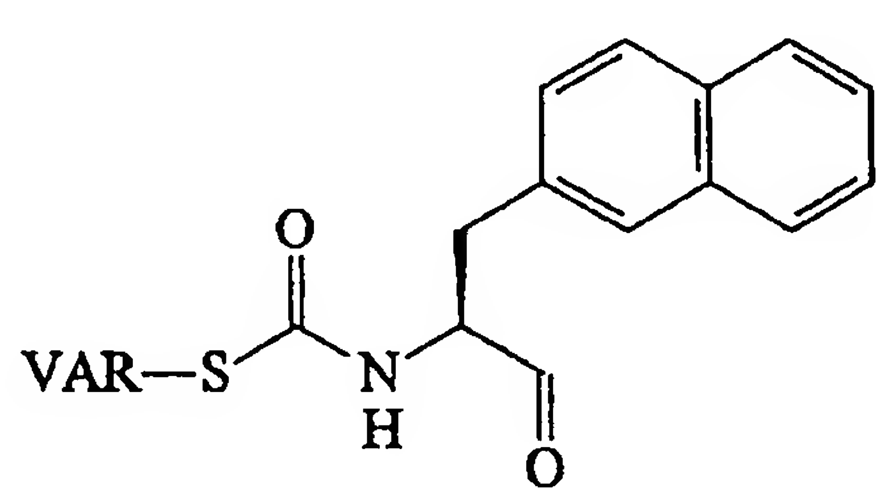
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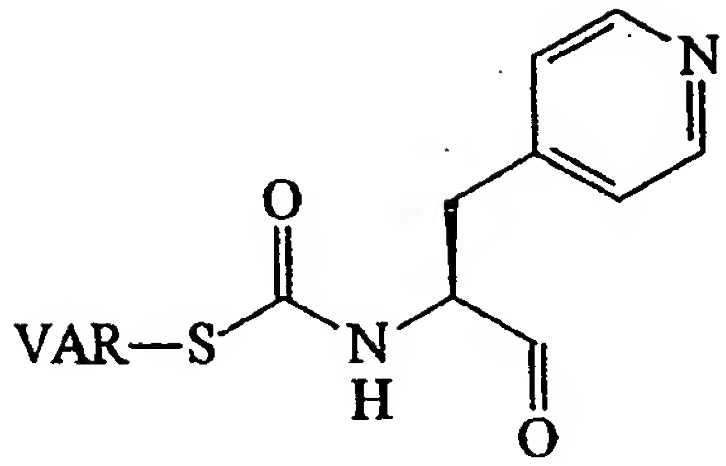
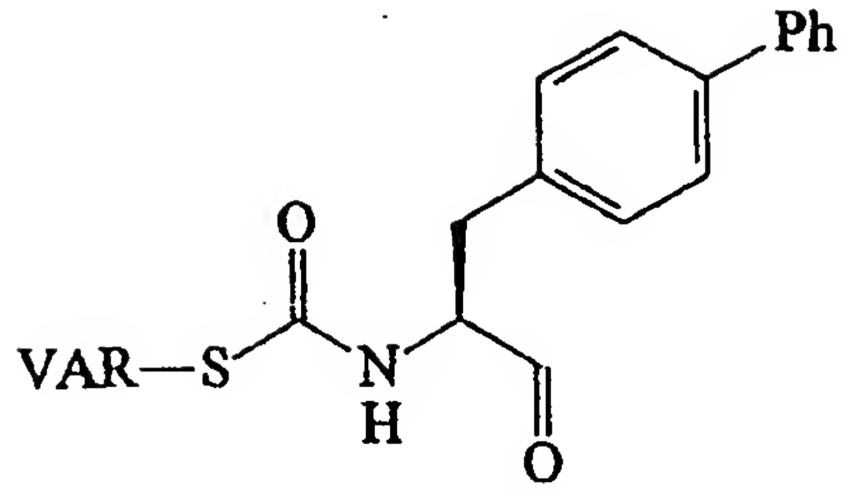
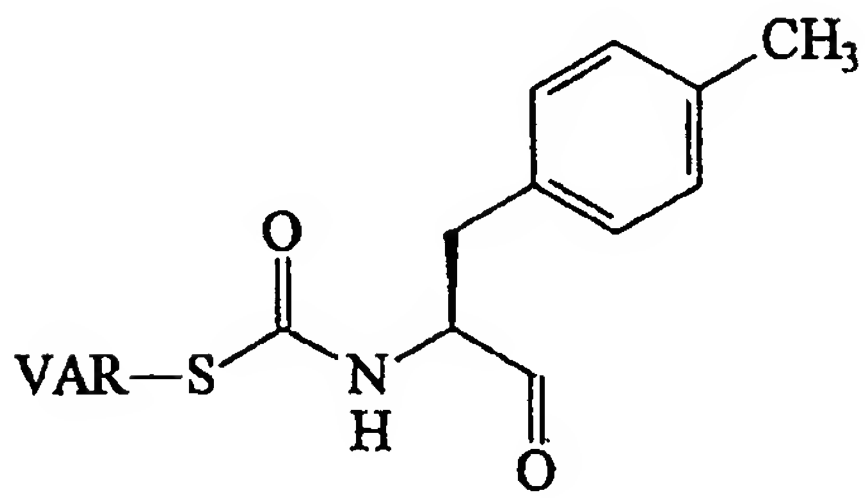
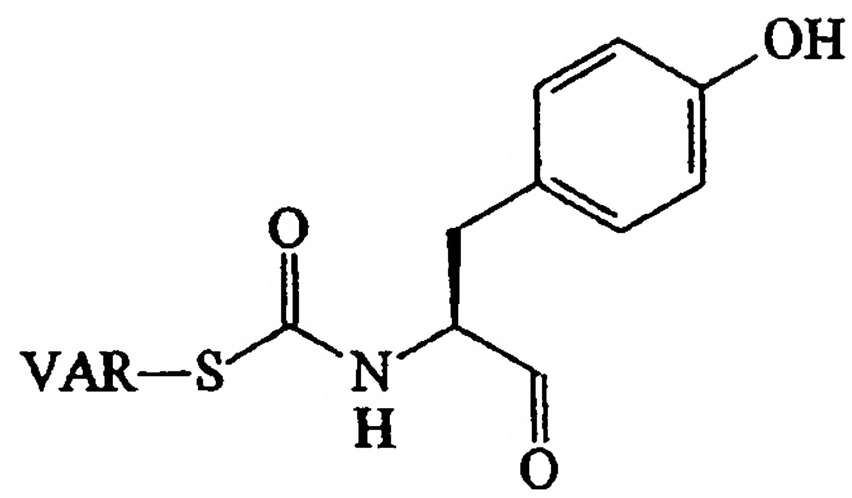
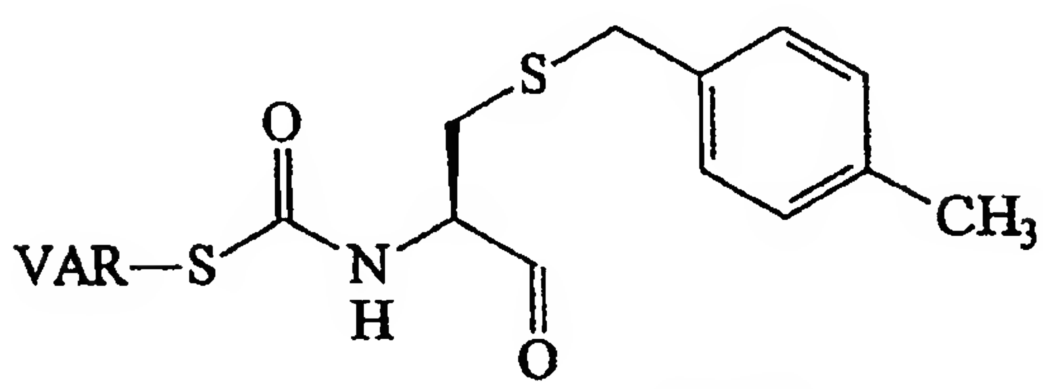
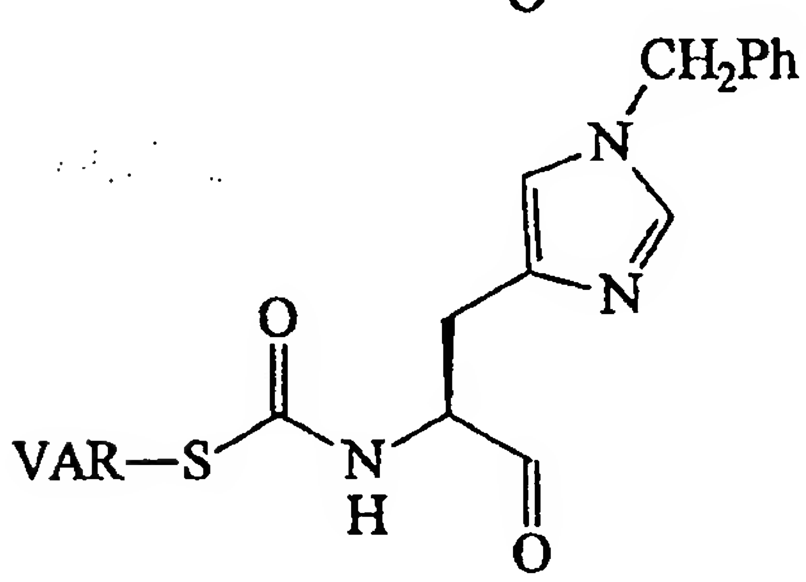
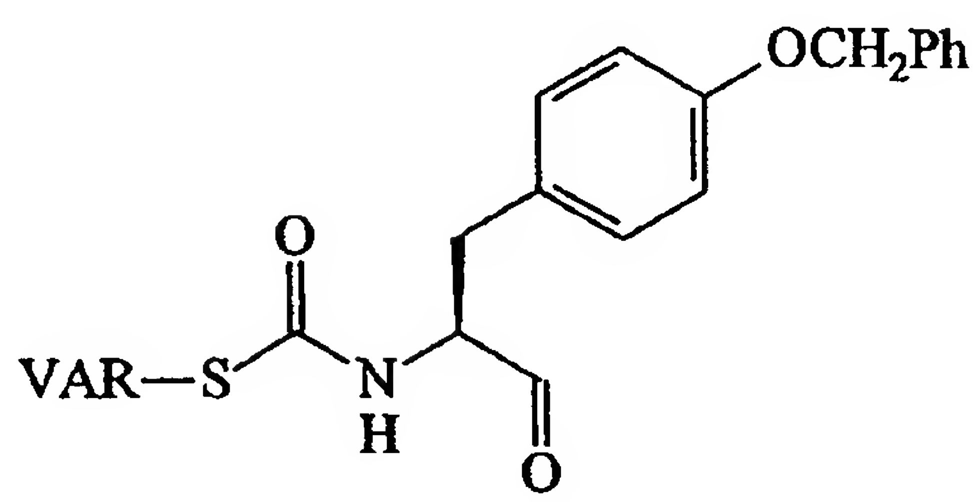
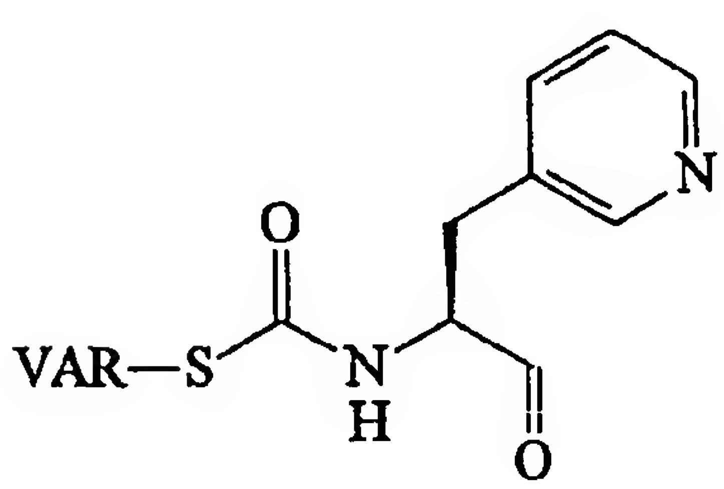
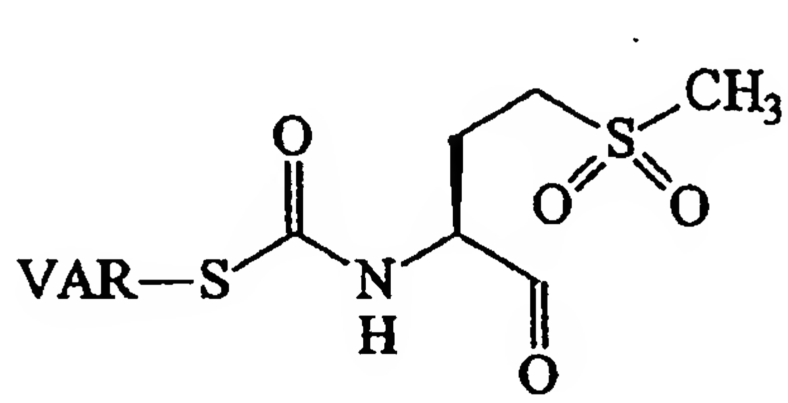
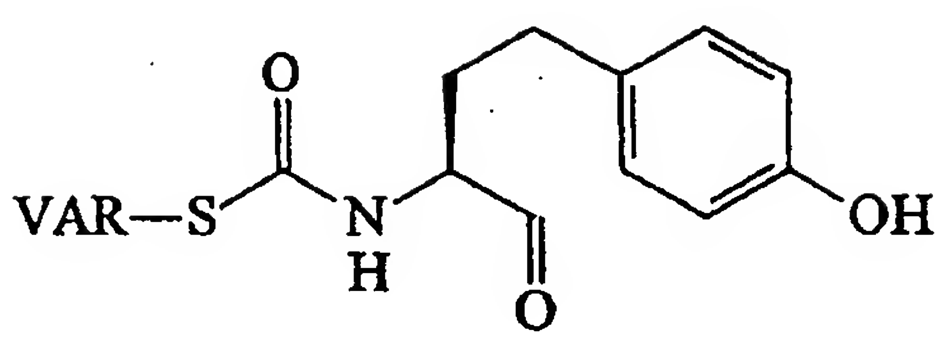
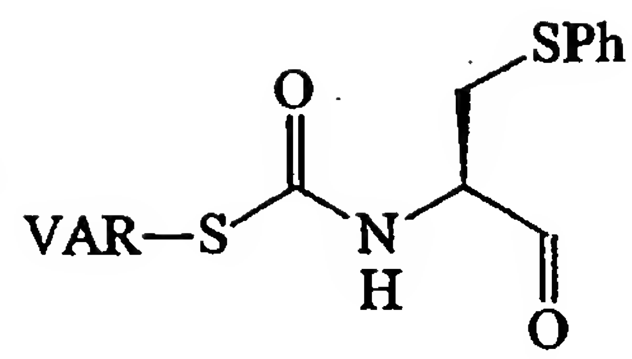
 ;  ;

 ;  ;

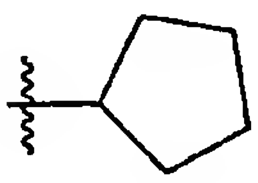
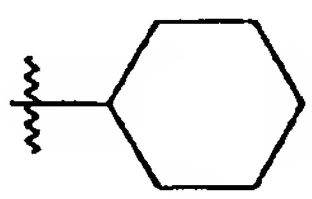
 ;

 ;  ;

 ;  ;

 ; and  ,

wherein VAR is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH_2Ph$,  , and  ,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

29. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof; and

(b) a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

30. A method of treating a mammalian disease condition mediated by picornaviral protease activity, comprising: administering to a mammal for the purpose of said treating a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

31. A method of inhibiting the activity of a picornaviral 3C protease, comprising: contacting the picornaviral 3C protease for the purpose of said inhibiting with an effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

32. A method of inhibiting the activity of a rhinoviral protease, comprising: contacting the rhinoviral protease for the purpose of said inhibiting with an effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active

metabolite, or solvate thereof.

33. A compound according to claim 1, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof, wherein said antipicornaviral activity is antirhinoviral activity.

34. A compound according to claim 1, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof, wherein said antipicornaviral activity is anticoxsackieviral activity.

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/US 98/26583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/027 C07C271/22 C07D233/70 A61K38/05 A61K31/415
A61K31/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 43305 A (AGOURON PHARMA) 20 November 1997 see the whole document ---	1-34
P,X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 2. Peptide structure-activity studies." JOURNAL OF MEDICINAL CHEMISTRY, (1998 JUL 16) 41 (15) 2819-34. JOURNAL CODE: JOF. ISSN: 0022-2623., XP002100727 United States see the whole document ---	1-34

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 1999	20/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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INTERNATIONAL SEARCH REPORT

Int. ...tional Application No
PCT/US 98/26583

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 1. Michael acceptor structure-activity studies." JOURNAL OF MEDICINAL CHEMISTRY, (1998 JUL 16) 41 (15) 2806-18. JOURNAL CODE: JOF. ISSN: 0022-2623., XP002100728 United States see the whole document -----	1-34

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INTERNATIONAL SEARCH REPORT

...ernational application No.

PCT/US 98/26583

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claims 30-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. .tional Application No
PCT/US 98/26583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9743305 A	20-11-1997	US 5856530 A	05-01-1999
		AU 3005997 A	05-12-1997
		CA 2254343 A	20-11-1997
		EP 0910572 A	28-04-1999

CORRECTED VERSION*

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/027, C07C 271/22, C07D 233/70, A61K 38/05, 31/415, 31/27 — A1

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(22) International Filing Date: 15 December 1998 (15.12.98)

(30) Priority Data:
08/991,739 16 December 1997 (16.12.97) US

(71) Applicant: AGOURON PHARMACEUTICALS, INC. [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037-1022 (US).

(72) Inventors: WEBBER, Stephen, E.; 3884 Mt. Abraham Avenue, San Diego, CA 92111 (US). DRAGOVICH, Peter, S.; 1372 Blue Heron Avenue, Encinitas, CA 92024 (US). PRINS, Thomas, J.; 2448 Oxford Avenue, Cardiff, CA 92007 (US). LITTLEFIELD, Ethel, S.; 9934 Parkdale Avenue, San Diego, CA 92126 (US). MARAKOVITS, Joseph, T.; 1449 Via Terrassa, Encinitas, CA 92024 (US). BABINE, Robert, E.; 7973 Amargosa Drive, Carlsbad, CA 92009 (US).

(74) Agents: GARRETT, Arthur, S.; Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., 1300 I Street, N.W., Washington, DC 20005-3315 (US) et al.

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTIPICORNAVIRAL COMPOUNDS AND METHODS FOR THEIR USE AND PREPARATION

(57) Abstract

Picornaviral 3C protease inhibitors, obtainable by chemical synthesis, inhibit or block the biological activity of picornaviral 3C proteases. These compounds, as well as pharmaceutical compositions that contain these compounds, are suitable for treating patients or hosts infected with one or more picornaviruses. Several novel methods and intermediates can be used to prepare the novel picornaviral 3C protease inhibitors of the present invention.

*(Referred to in PCT Gazette No. 39/1999, Section II)

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EE	Estonia						

ANTIPICORNAVIRAL COMPOUNDS AND METHODS FOR THEIR USE AND PREPARATION

RELATED APPLICATION DATA

This application relates to U.S. Patent Application Nos. 08/825,331, filed March 28, 1997, and 08/850,398, filed May 2, 1997. Additionally, this application relates to U.S. Provisional Patent Application No. 60/046,204, filed May 12, 1997. Each of these U.S. patent applications relates to antipicornaviral compounds, compositions containing them, and methods for their production and use. Each of these applications also is entirely incorporated herein by reference. Additionally, this application relates to a concurrently filed U.S. patent application entitled "Antipicornaviral Compounds, Compositions Containing Them, and Methods for Their Use," U.S. Patent Appln. No. 08/991,282, filed in the names of inventors Peter S. Dragovich, Thomas J. Prins, and Ru Zhou (Attorney Docket No. 1074.0176-01). This concurrently filed application also is entirely incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention pertains to the discovery and use of new compounds that inhibit the enzymatic activity of picornaviral 3C proteases, specifically rhinovirus proteases ("RVPs"), as well as retard viral growth in cell culture.

The picornaviruses are a family of tiny non-enveloped positive stranded RNA containing viruses that infect humans and other animals. These viruses include the human rhinoviruses, human polioviruses, human coxsackieviruses, human echoviruses, human and bovine enteroviruses, encephalomyocarditis viruses, menigovirus, foot and mouth viruses, hepatitis A virus, and others. The human rhinoviruses are a major cause of the common cold. To date, there are no effective therapies to cure the common cold, only treatments that relieve the symptoms.

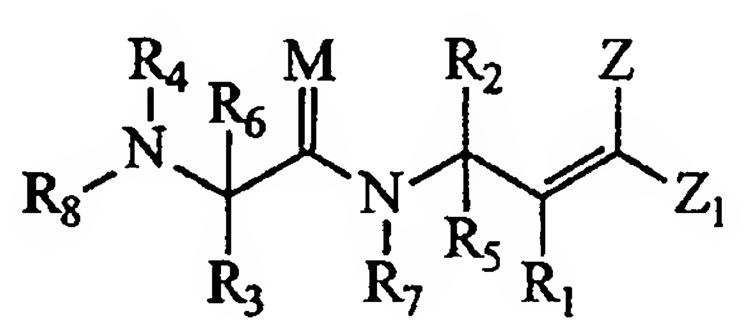
Picornaviral infections may be treated by inhibiting the proteolytic 3C enzymes. These enzymes are required for the natural maturation of the picornaviruses. They are responsible for the autocatalytic cleavage of the genomic, large polyprotein into the essential viral proteins. Members of the 3C protease family are cysteine proteases, where the sulfhydryl group most often cleaves the glutamine-glycine amide bond. Inhibition of 3C proteases is believed to block proteolytic cleavage of the polyprotein, which in turn can retard the maturation and replication of the viruses by interfering with viral particle production.

Therefore, inhibiting the processing of this cysteine protease with selective, small molecules that are specifically recognized, should represent an important and useful approach to treat or cure viral infections of this nature and, in particular, the common cold.

SUMMARY OF THE INVENTION

The present invention is directed to compounds that function as picornaviral 3C protease inhibitors, particularly those that have antiviral activity. It is further directed to the preparation and use of such 3C protease inhibitors. The Inventors demonstrate that the compounds of the present invention bind to rhinovirus 3C proteases and preferably have antiviral cell culture activity. The enzymatic inhibition assays used reveal that these compounds can bind irreversibly, and the cell culture assays demonstrate that these compounds can possess antiviral activity.

The present invention is directed to compounds of the formula (I):



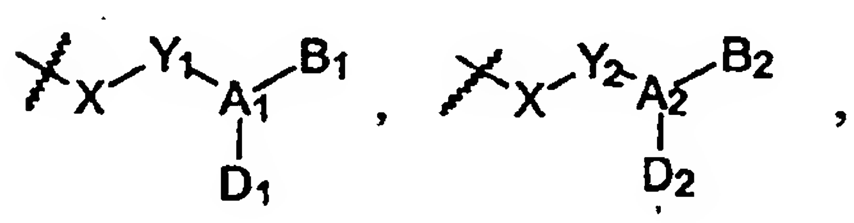
(I),

wherein:

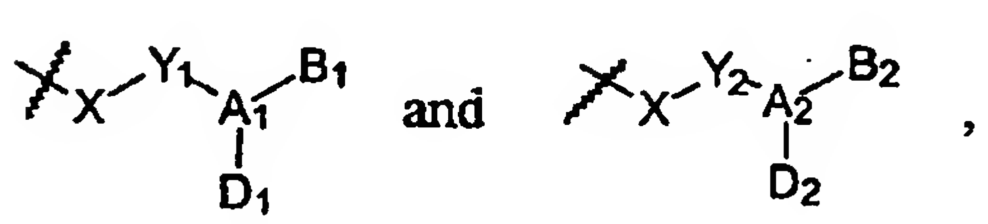
M is O or S;

R_1 is H, F, an alkyl group, OH, SH, or an O-alkyl group;

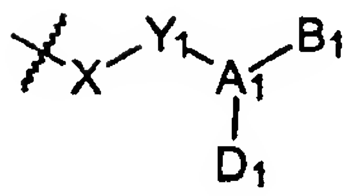
R_2 and R_5 are independently selected from H,



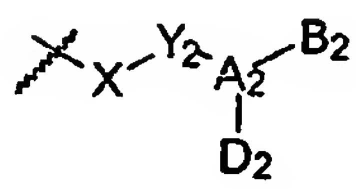
or an alkyl group, wherein the alkyl group is different from



with the proviso that at least one of R_2 or R_5 must be

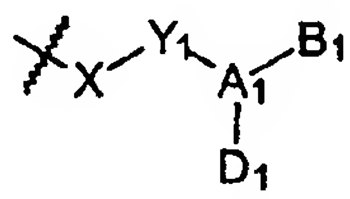


or



,

and wherein, when R_2 or R_5 is



X is =CH or =CF and Y_1 is =CH or =CF,

or X and Y_1 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_1 is $-CH-$, $-CF-$, or $-C(alkyl)-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_1 is $-O-$, $-S-$, $-NR_{12}-$, $-C(R_{13})(R_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR_{13}R_{14})-$,

wherein R_{12} is H or alkyl, and R_{13} and R_{14} independently are H, F, or an alkyl group, or, together with the atoms to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

A_1 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_1 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and

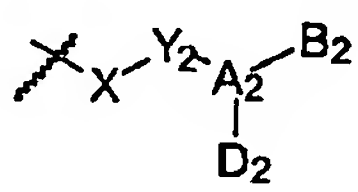
B_1 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N;

and further wherein, when R_2 or R_5 is



X is =CH or =CF and Y_2 is =C, =CH or =CF,

or X and Y_2 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_2 is $-CH-$, $-CF-$, or $-C(alkyl)-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_2 is $-O-$, $-S-$, $-N(R'_{12})-$, $-C(R'_{13})(R'_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR'_{13}R'_{14})-$,

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR'_{13}$, $-NR'_{13}R'_{14}$, $-C(O)-R'_{13}$, $-SO_2R'_{13}$, or $-C(S)R'_{13}$, and R'_{13} and R'_{14} independently are H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

A_2 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and

B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and further wherein any combination of Y_2, A_2, B_2, and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

R_3 and R_6 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{17}$, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or, R_3 and R_6, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

R_4 is any suitable organic moiety, or R_4 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

R_7 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or R_7 together with R_3 or R_6 and the atoms to which they are attached form a heterocycloalkyl group;

R_8 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-NR_{29}R_{30}$, $-OR_{29}$, or $-C(O)R_{29}$,

wherein R_{29} and R_{30} each independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

or R_8 together with R_4 and the nitrogen atom to which they are attached form a heterocycloalkyl group or a heteroaryl group, or R_8 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$,

$-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

or Z_1, as defined above, together with R_1, as defined above, and the atoms to which Z_1 and R_1 are bonded, form a cycloalkyl or heterocycloalkyl group,

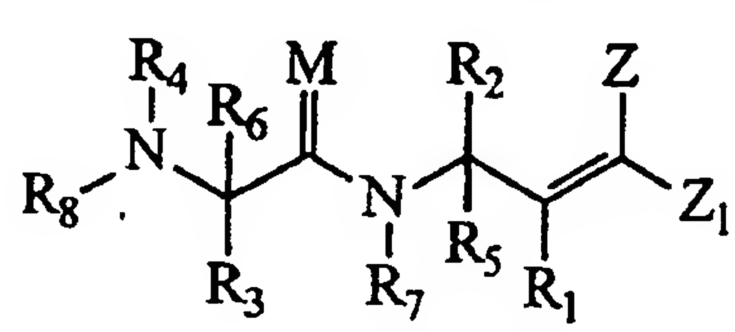
or Z and Z_1, both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

with the proviso that when R_7 is H, R_8 is a moiety other than H;

and pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof; and wherein these compounds, pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the formula I

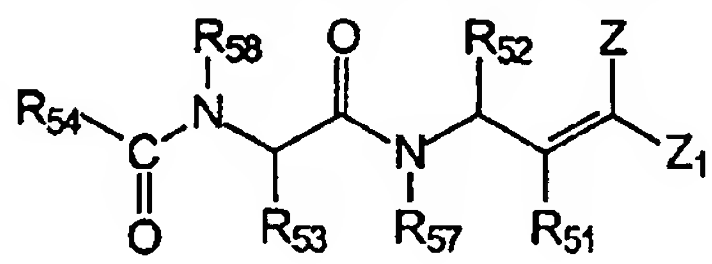


(I),

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, M, Z, and Z_1 are as defined above, and to the pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof, where these compounds, pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates preferably have antipicornaviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay, and more preferably antirhinoviral activity with an EC_{50}

less than or equal to 100 μM in the HI-HeLa cell culture assay and/or anticoxsachieviral activity with an EC_{50} less than or equal to 100 μM in the HI-HeLa cell culture assay.

The present invention preferably relates to compounds of the formula II:

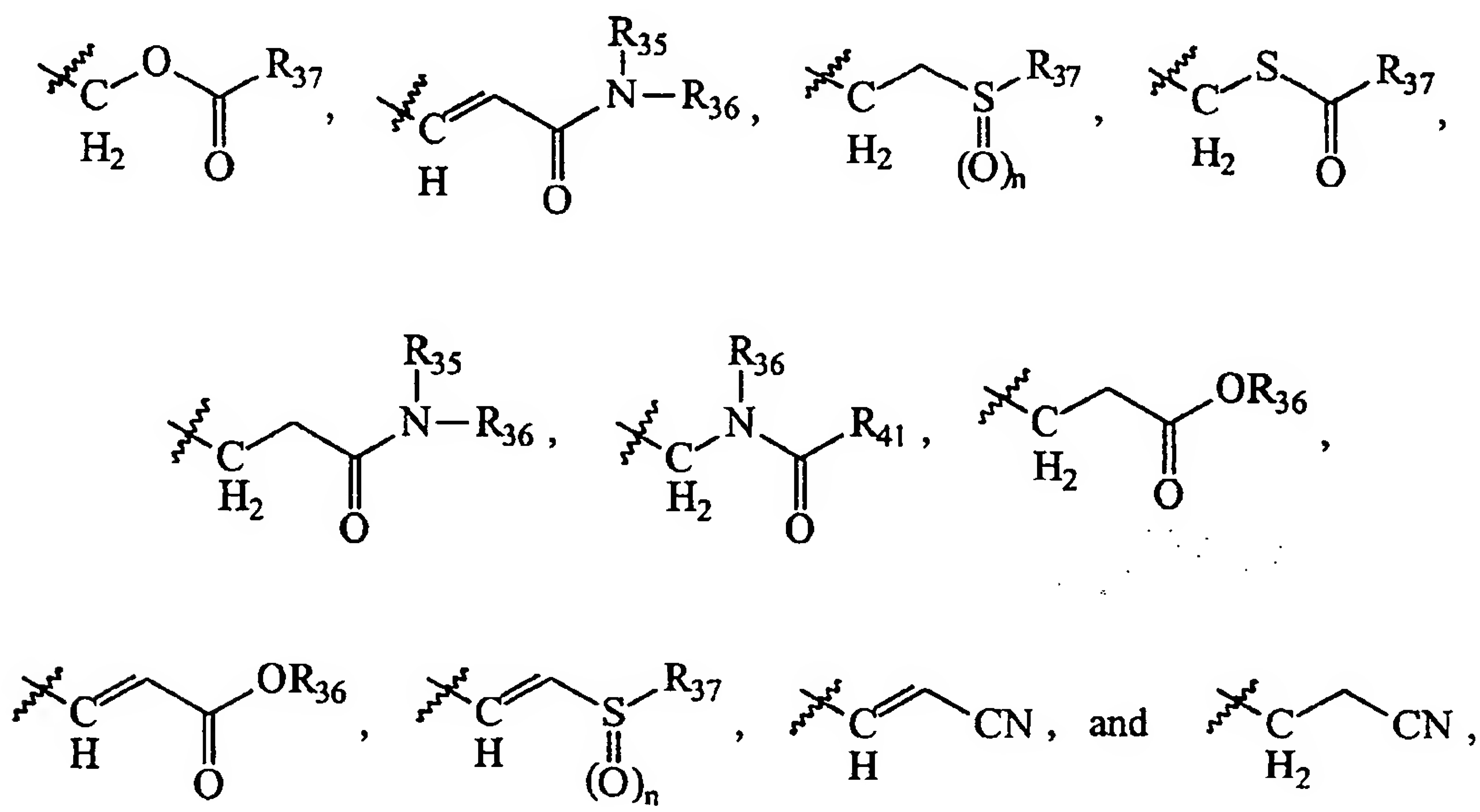


(II),

wherein:

R_{51} is H, F, or an alkyl group;

R_{52} is selected from one of the following moieties:



wherein:

R_{35} is H, an alkyl group, an aryl group, $-OR_{38}$, or $-NR_{38}R_{39}$,

wherein R_{38} and R_{39} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

R_{36} is H or an alkyl group,

or R_{35} and R_{36}, together with the nitrogen atom to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$, wherein R_{38} and R_{39} are as defined above;

R_{41} is H, an alkyl group, an aryl group, $-OR_{38}$, $-SR_{39}$, $-NR_{38}R_{39}$, $-NR_{40}NR_{38}R_{39}$, or $-NR_{38}OR_{39}$, or R_{41} and R_{36}, together with the atom(s) to which they are attached, form a heterocycloalkyl group;

wherein R_{38} and R_{39} are as defined above, and R_{40} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

n is 0, 1 or 2;

R_{53} is H or an alkyl group;

R_{54} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl group, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group;

or R_{54} together with R_{58} and the nitrogen atom to which they are attached form a heterocycloalkyl group or a heteroaryl group;

R_{57} is H or an alkyl group;

R_{58} is H, an alkyl group, a cycloalkyl group, $-OR_{70}$, or $NR_{70}R_{71}$, wherein R_{70} and R_{71} are independently H or an alkyl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or wherein Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group;

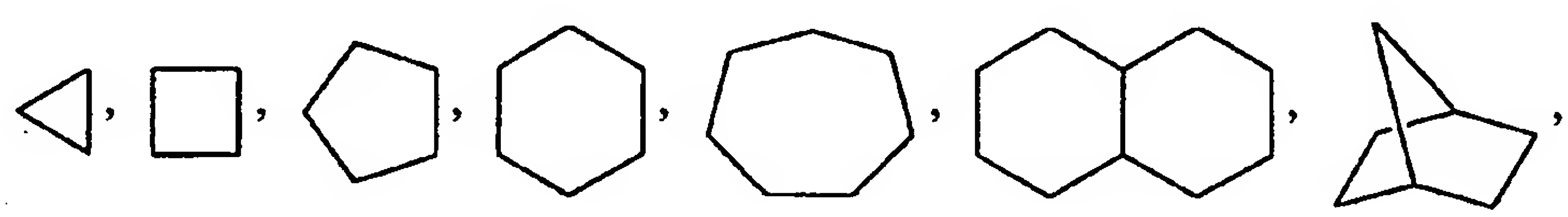
with the proviso that when R_{57} is H, R_{58} is a moiety other than H;

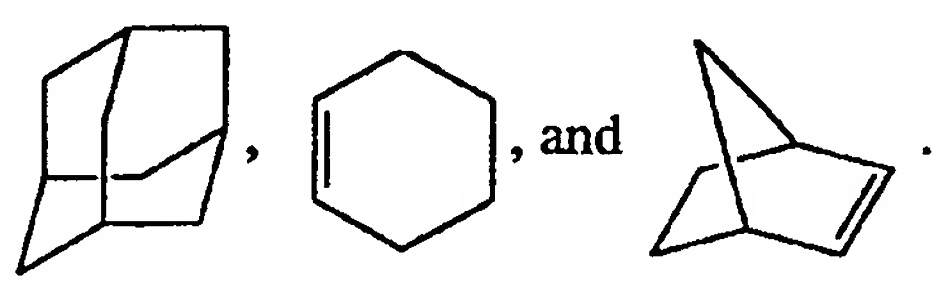
and pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates thereof.

As used in the present application, the following definitions apply:

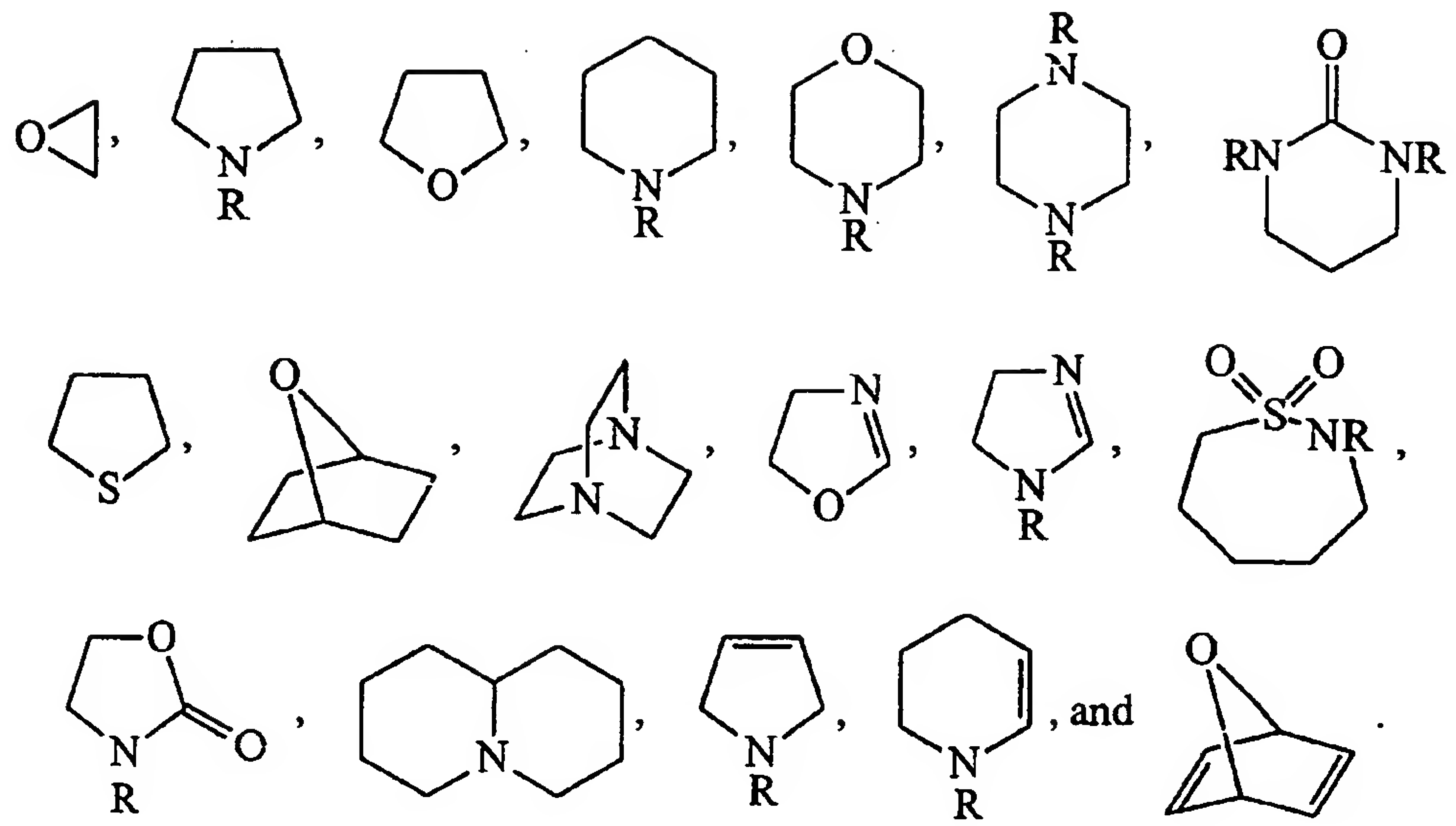
An "alkyl group" is intended to mean a straight or branched chain monovalent radical of saturated and/or unsaturated carbon atoms and hydrogen atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, pentenyl, butenyl, propenyl, ethynyl, butynyl, propynyl, pentynl, hexynyl, and the like, which may be unsubstituted (i.e., containing only carbon and hydrogen) or substituted by one or more suitable substituents as defined below.

A "cycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon ring atoms, each of which may be saturated or unsaturated, and which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more heterocycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:

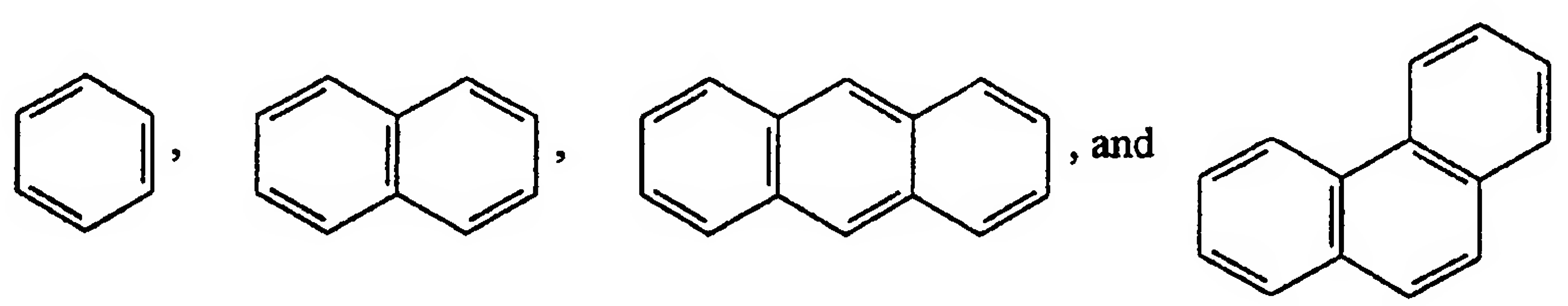




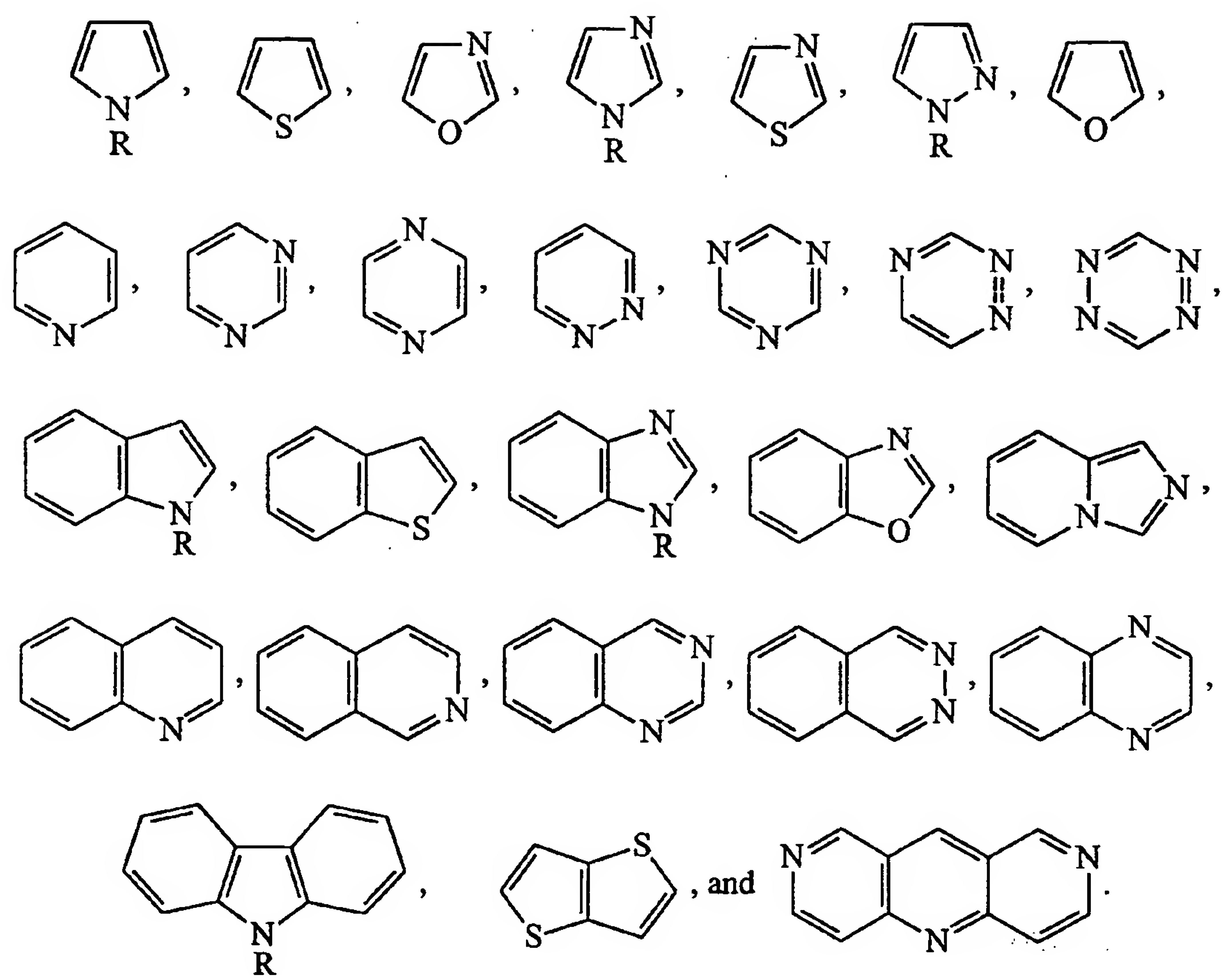
A "heterocycloalkyl group" is intended to mean a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or unsaturated, containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, and which includes 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein the radical is unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, aryl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heterocycloalkyl groups include, but are not limited to the following moieties:



An "aryl group" is intended to mean an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing 6, 10, 14, or 18 carbon ring atoms, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of aryl groups include, but are not limited to, the following moieties:



A "heteroaryl group" is intended to mean an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms, including 1, 2, 3, 4, or 5 heteroatoms selected from nitrogen, oxygen, and sulfur, which may be unsubstituted or substituted by one or more suitable substituents as defined below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups, or aryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of heteroaryl groups include, but are not limited to, the following moieties:



An "acyl group" is intended to mean a $-C(O)-R$ radical, wherein R is any suitable substituent as defined below.

A "thioacyl group" is intended to mean a $-C(S)-R$ radical, wherein R is any suitable substituent as defined below.

A "sulfonyl group" is intended to mean a $-SO_2R$ radical, wherein R is any suitable substituent as defined below.

The term "suitable substituent" is intended to mean any of the substituents recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable substituents include, but are not limited to, hydroxy groups, oxo groups, alkyl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, carboxy groups, amino

groups, alkylamino groups, dialkylamino groups, carbamoyl groups, aryloxy groups, heteroarlyoxy groups, arylthio groups, heteroarylthio groups, and the like.

The term "suitable organic moiety" is intended to mean any organic moiety recognizable, such as by routine testing, to those skilled in the art as not adversely affecting the inhibitory activity of the inventive compounds. Illustrative examples of suitable organic moieties include, but are not limited to, hydroxy groups, alkyl groups, oxo groups, cycloalkyl groups, heterocycloalkyl groups, aryl groups, heteroaryl groups, acyl groups, sulfonyl groups, mercapto groups, alkylthio groups, alkoxy groups, carboxy groups, amino groups, alkylamino groups, dialkylamino groups, carbamoyl groups, arylthio groups, heteroarylthio groups, and the like.

A "hydroxy group" is intended to mean the radical -OH.

An "amino group" is intended to mean the radical $-NH_2$.

An "alkylamino group" is intended to mean the radical -NHR where R is an alkyl group as defined above.

A "dialkylamino group" is intended to mean the radical $-NR_aR_b$ where R_a and R_b are each independently an alkyl group as defined above.

An "alkoxy group" is intended to mean the radical -OR where R is an alkyl group as defined above, for example, methoxy, ethoxy, propoxy, and the like.

An "alkoxycarbonyl group" is intended to mean the radical -C(O)OR where R is an alkyl group as defined above.

An "alkylsulfonyl group" is intended to mean the radical $-SO_2R$ where R is an alkyl group as defined above.

An "alkylaminocarbonyl group" is intended to mean the radical -C(O)NHR where R is an alkyl group as defined above.

A "dialkylaminocarbonyl group" is intended to mean the radical $-C(O)NR_aR_b$ where R_a and R_b are each independently an alkyl group as defined above.

A "mercapto group" is intended to mean the radical -SH.

An "alkylthio group" is intended to mean the radical -SR where R is an alkyl group as defined above.

A "carboxy group" is intended to mean the radical -C(O)OH.

A "carbamoyl group" is intended to mean the radical $-C(O)NH_2$.

An "aryloxy group" is intended to mean the radical $-OR_c$ where R_c is an aryl group as defined above.

A "heteroarlyoxy group" is intended to mean the radical $-OR_d$ where R_d is a heteroaryl group as defined above.

An "arylthio group" is intended to mean the radical $-SR_c$ where R_c is an aryl group as defined above.

A "heteroarylthio group" is intended to mean the radical $-SR_d$ where R_d is a heteroaryl group as defined above.

A "pharmaceutically acceptable prodrug" is intended to mean a compound that may be converted under physiological conditions or by solvolysis to a compound of formula I.

A "pharmaceutically acceptable active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a compound of formula I.

A "pharmaceutically acceptable solvate" is intended to mean a solvate that retains the biological effectiveness and properties of the biologically active components of compounds of formula I.

Examples of pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

A "pharmaceutically acceptable salt" is intended to a mean a salt that retains the biological effectiveness and properties of the free acids and bases of compounds of formula I and that is not biologically or otherwise undesirable.

Examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acids such as glucuronic acid and galacturonic acid, alpha-hydroxy acids such as citric acid and tartaric acid, amino acids such as aspartic acid and glutamic acid, aromatic acids such as benzoic acid and cinnamic acid, sulfonic acids such a p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary and tertiary amines, and cyclic amines such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention.

The inventive compounds may exist as single stereoisomers, racemates and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive compounds are used in optically pure form.

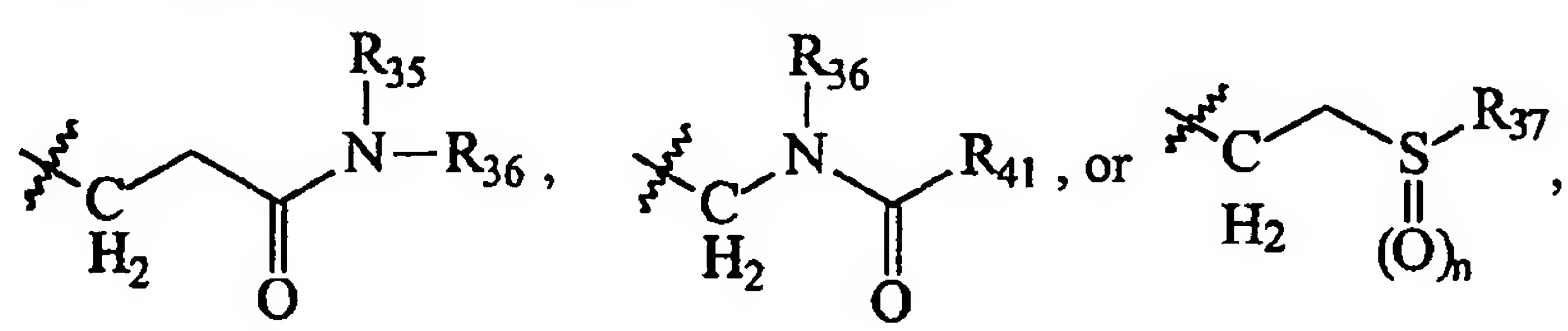
As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound which comprises at least a sufficient amount of a single enantiomer to yield a compound having the desired pharmacological activity. Preferably, "optically pure" is intended to mean a compound that comprises at least 90% of a single isomer (80% enantiomeric excess), preferably at least 95% (90% e.e.), more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

Preferably in the above formulas I and II, R_1 and R_{51} are H or F. Preferably in the compounds of formula I, at least one of R_4 and R_8 is an acyl group or a sulfonyl group. Preferably in the above formulas I and II, D_1 and D_2 are $-OR_{25}$, =O, =S, ≡N, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group, and more preferably D_1 and D_2 are =O. Preferably A_1 and A_2 are C, CH, S, or S(O), and more preferably A_1 and A_2 are C.

Preferably B_1 and B_2 are $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein R_{17} and R_{18}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group.

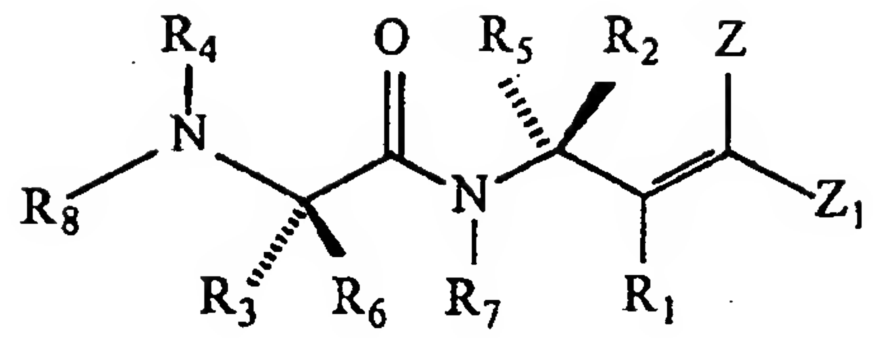
Preferably Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$; wherein R_{21}, R_{22}, and R_{23} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group, or wherein any two of R_{21}, R_{22}, and R_{23}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group, or Z and Z_1, together with the atoms to which they are attached, form a heterocycloalkyl group. Preferably M is O.

Preferably R_{52} is one of the following moieties:



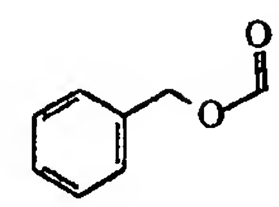
wherein R_{35}, R_{36}, R_{37}, R_{41}, and n are as defined above.

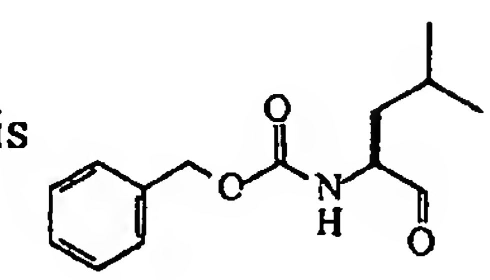
Compounds according to formula I include those described below, where * indicates the point of attachment. For example, the invention includes compounds **1-17** having the formula Ia:

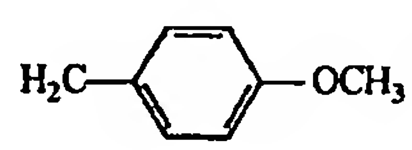


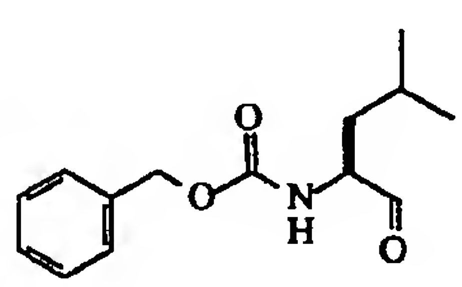
(Ia),

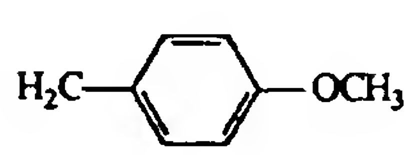
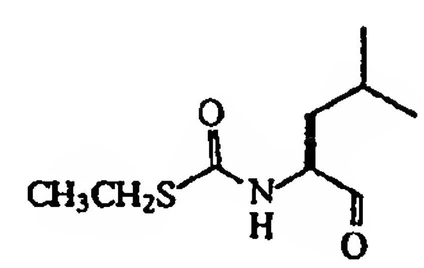
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

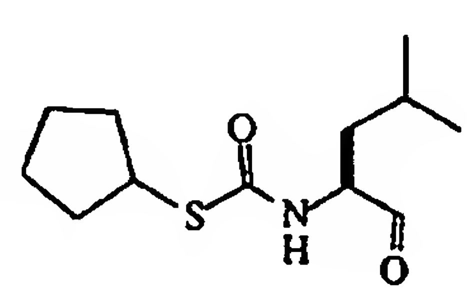
1. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

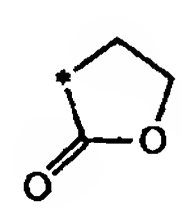
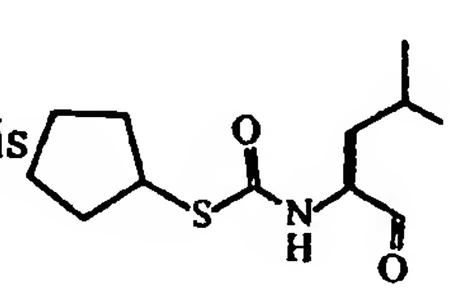
2. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

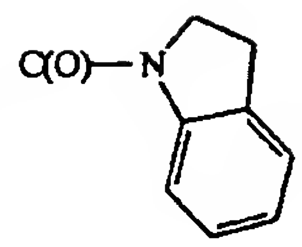
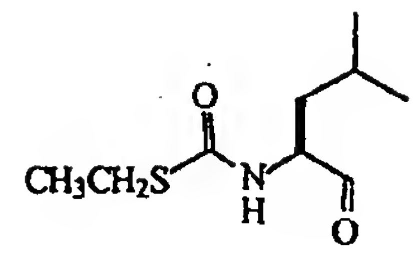
3. Z is H, Z_1 is $CO_2CH_2CH_3$, R_3 is  and

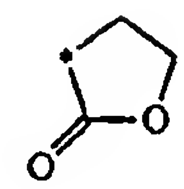
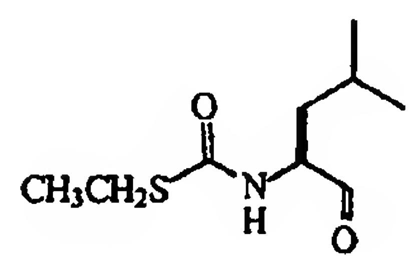
   R_8 is  ;

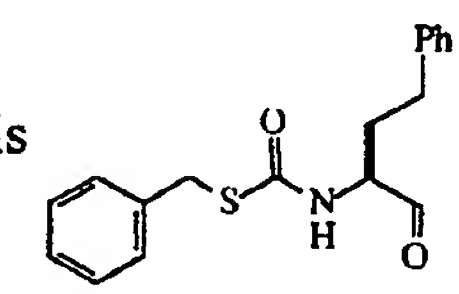
4. R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

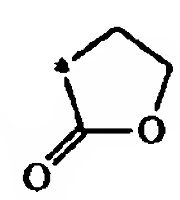
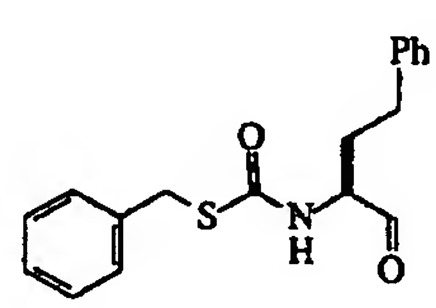
5. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

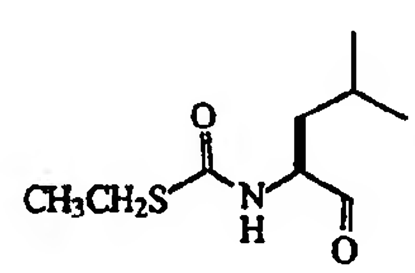
6. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group is preferably cis to the R_1 group), and R_8 is  ;

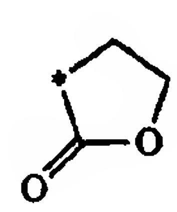
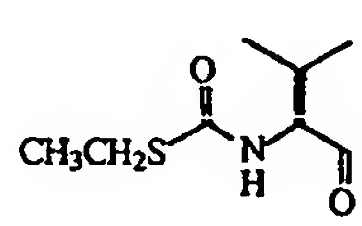
7. R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is ;

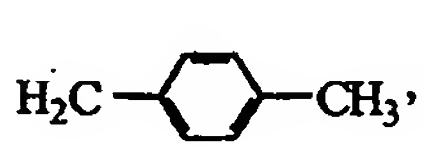
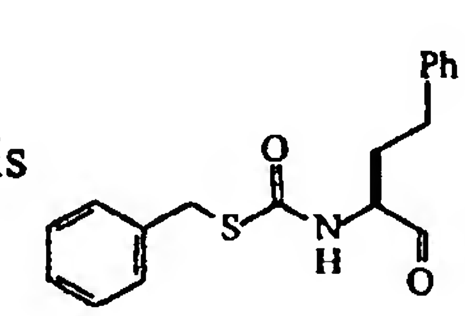
8. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group is preferably cis to the R_1 group), and R_8 is ;

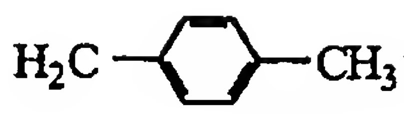
9. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

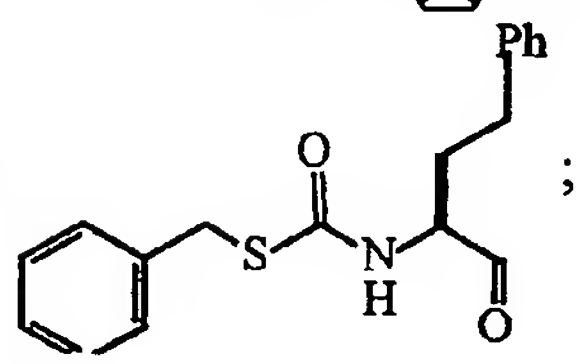
10. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group preferably is cis to the R_1 group), and R_8 is ;

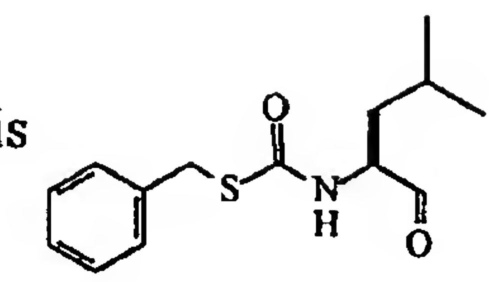
11. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

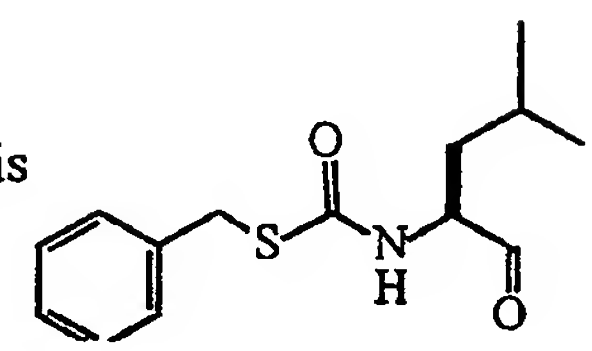
12. R_3 is CH_2Ph, Z and Z_1 together form  (where the C=O group preferably is cis to the R_1 group), and R_8 is ;

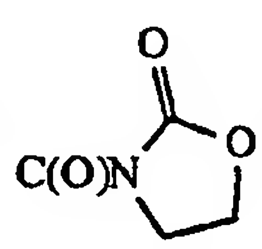
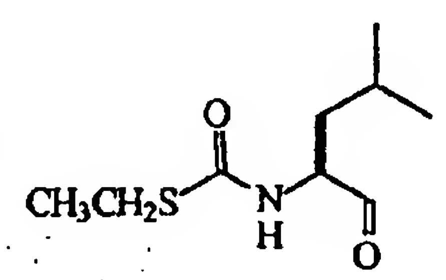
13. R_3 is , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

14. R_3 is , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and

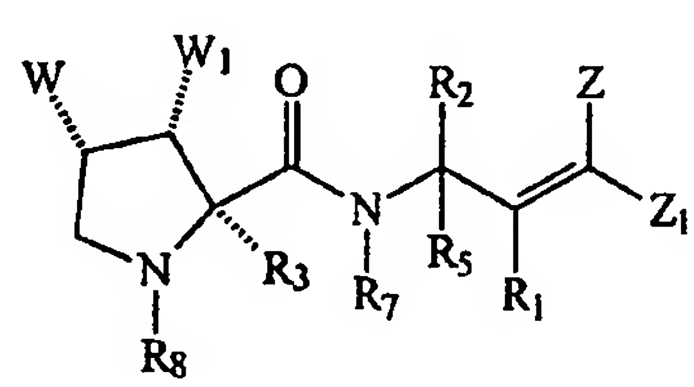
R_8 is  ;

15. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

16. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ; and

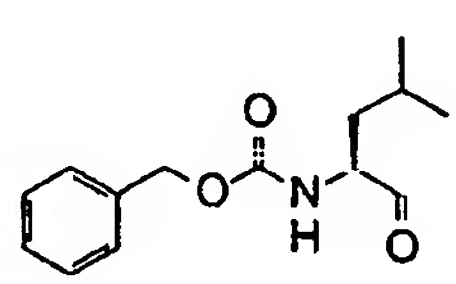
17. R_3 is CH_2Ph, Z is H, Z_1 is  and R_8 is  .

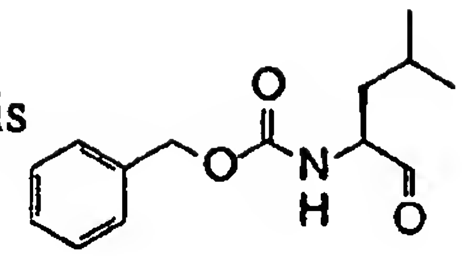
Additional compounds according to the invention include compounds **18–24** having the formula Ib:

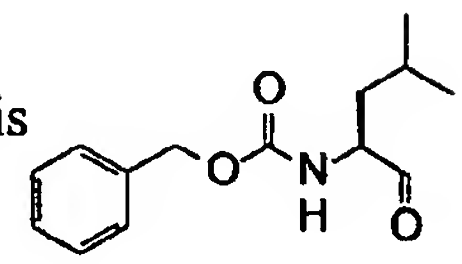


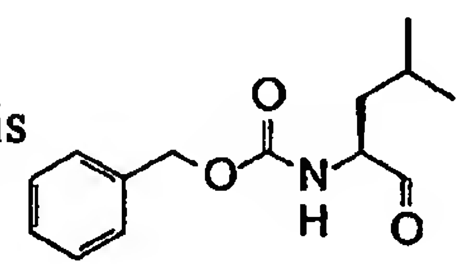
(Ib),

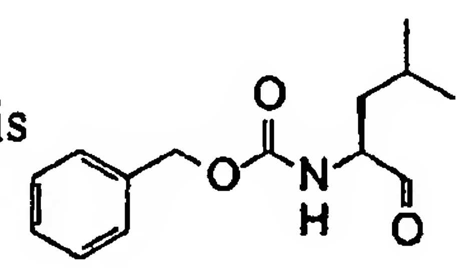
wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, and Z_1, W, W_1, and R_8 are selected from one of the following groups:

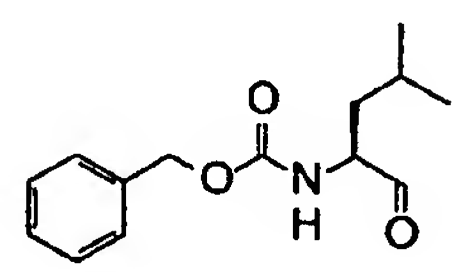
18. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is Ph, and R_8 is  ;

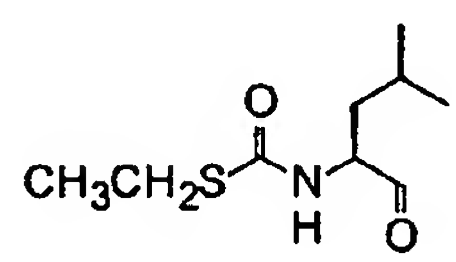
19. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  ;

20. Z_1 is $CO_2CH_2CH_3$, W is OCH_2Ph, W_1 is H, and R_8 is  ;

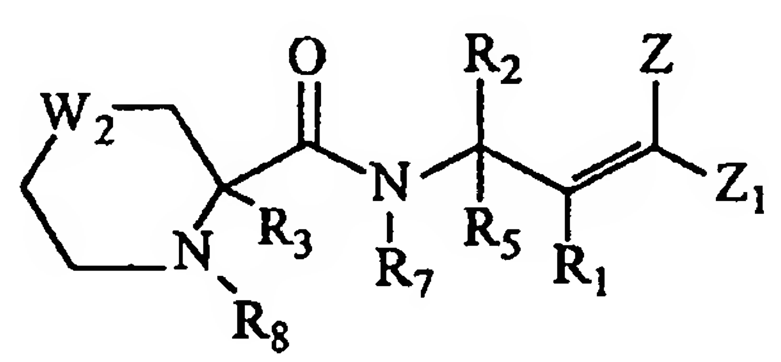
21. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is CH_3, and R_8 is  ;

22. Z_1 is $C(O)N(CH_3)OCH_3$, W is H, W_1 is Ph, and R_8 is  ;

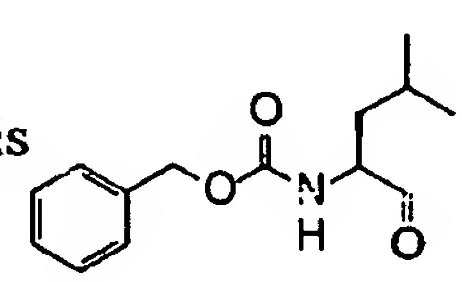
23. Z_1 is $CO_2CH_2CH_3$, W is $OC(CH_3)_3$, W_1 is H, and R_8 is  ; and

24. Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  .

The invention further includes compounds **25–29** having the formula Ic:

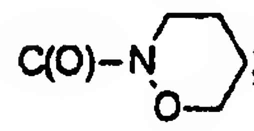


(Ic),

wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_8 is  , and

W_2 and Z_1 are selected from one of the following groups:

25. W_2 is CH_2 and Z_1 is $CO_2CH_2CH_3$;

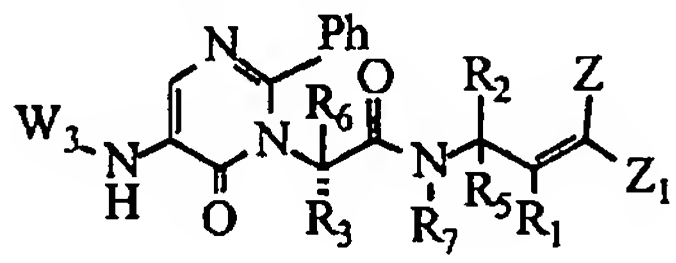
26. W_2 is CH_2 and Z_1 is ;

27. W_2 is NH and Z_1 is $CO_2CH_2CH_3$;

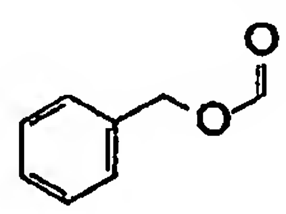
28. W_2 is NCH_2Ph and Z_1 is $CO_2CH_2CH_3$; and

29. W_2 is NSO_2Ph and Z_1 is $CO_2CH_2CH_3$.

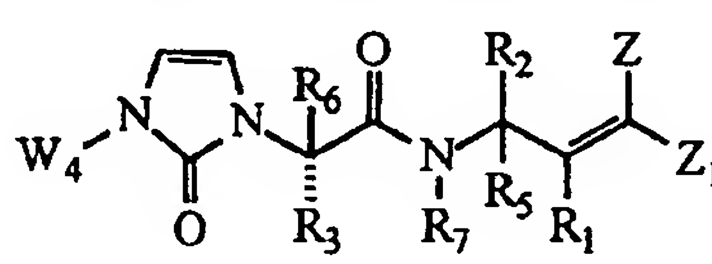
Additionally, the invention includes compounds **30** and **31** according to formula Id:



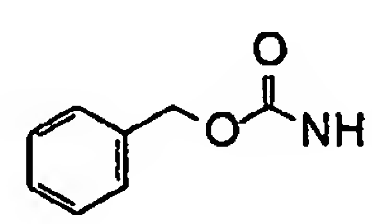
(Id),

wherein R_1, R_3, R_5, R_6, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_3 is  in Compound 30, and W_3 is H in Compound 31.

The invention also includes compounds **32** and **33** according to formula Ie:



(Ie),

wherein R_1, R_5, R_6, R_7, and Z are each H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z_1 is $CO_2CH_2CH_3$, and W_4 is H in Compound 32, and W_4 is  in Compound 33.

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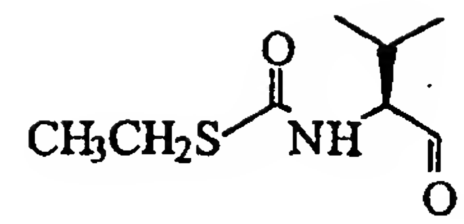
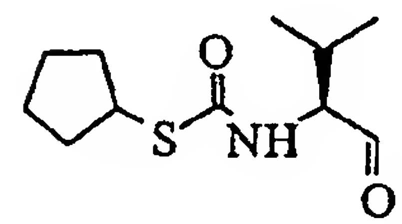
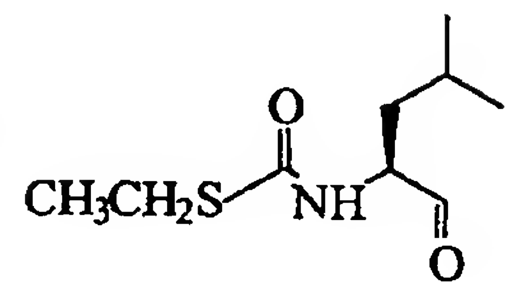
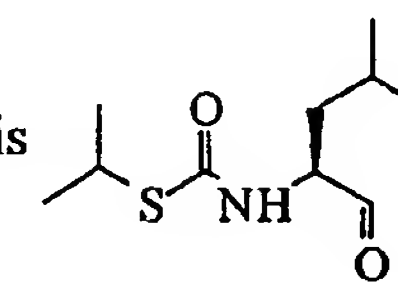
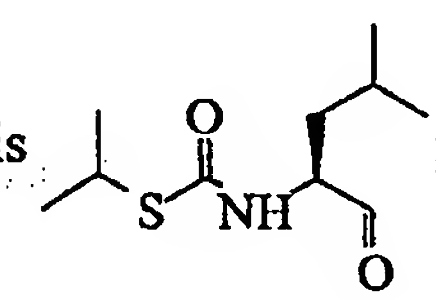
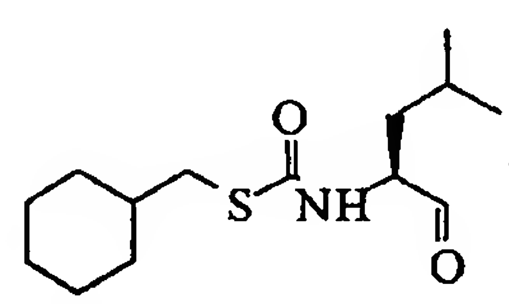
34. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

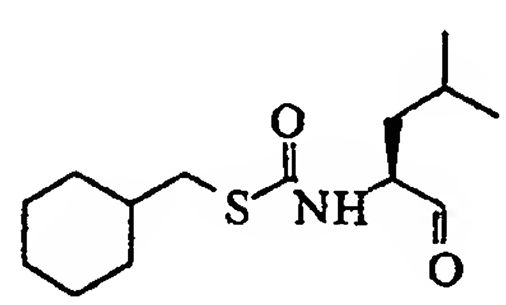
35. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

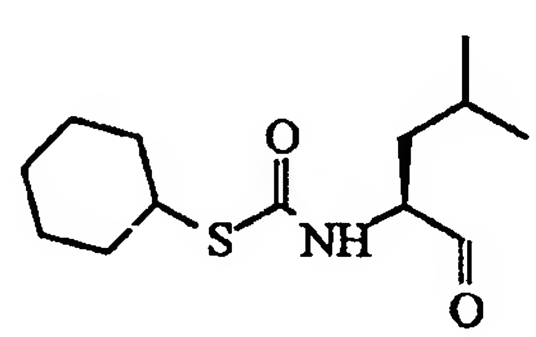
36. R_3 is CH_2Ph, Z is H, Z_1 is $C(O)N(CH_3)OCH_3$, and R_8 is  ;

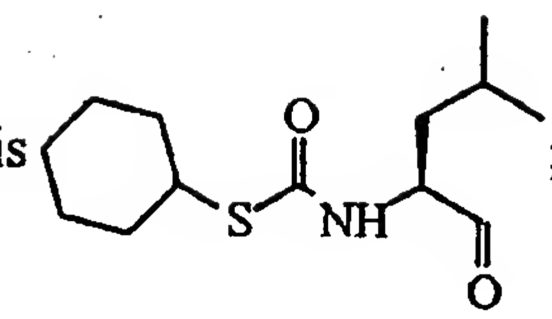
38. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

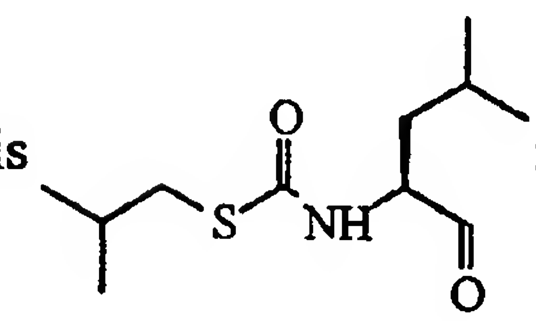
39. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

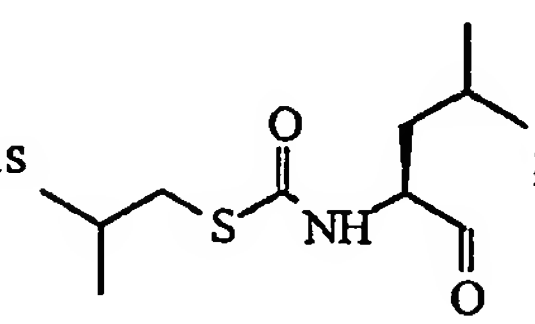
40. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

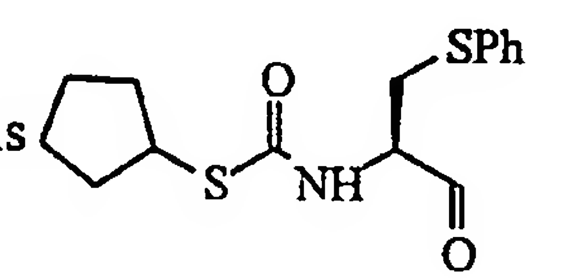
41. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

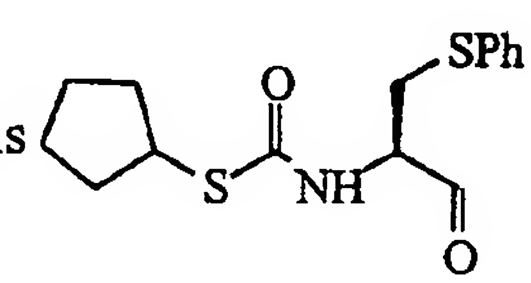
42. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

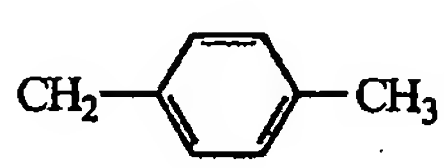
43. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

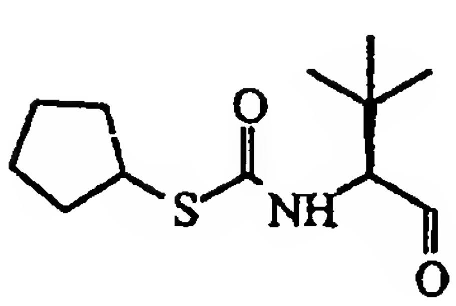
44. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

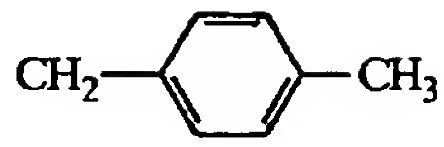
45. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

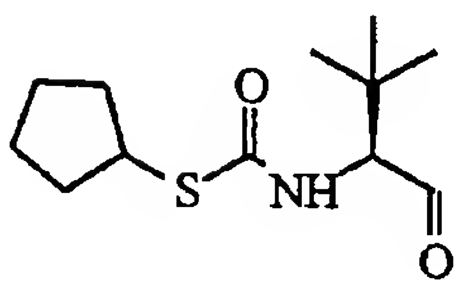
46. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

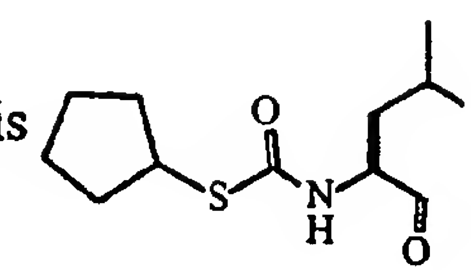
47. R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

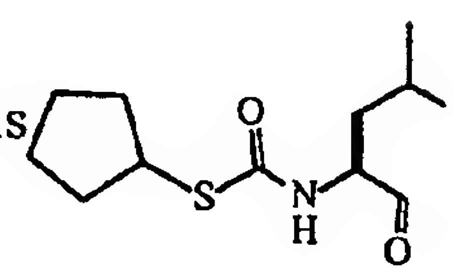
48. R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is

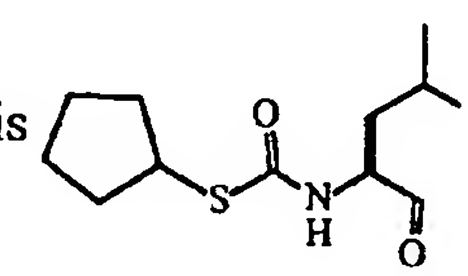
 ;

49. R_3 is  , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is

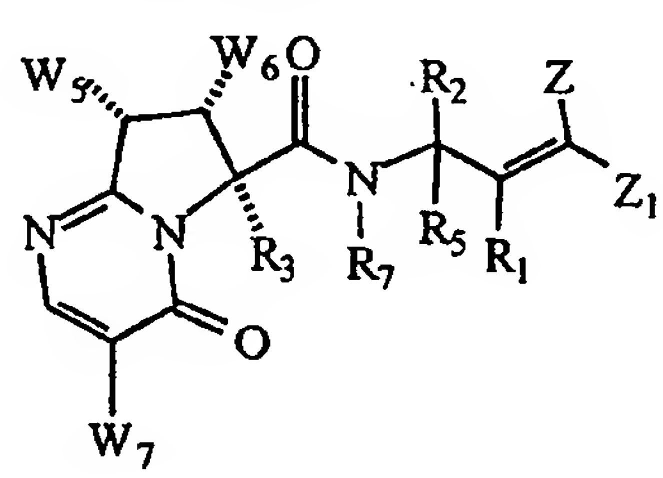
 ;

56. R_3 is CH_2Ph, Z is H, Z_1 is CO_2CH_2Ph, and R_8 is  ;

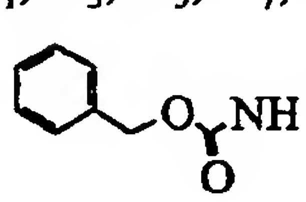
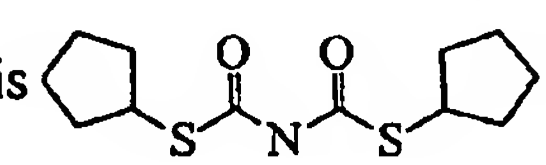
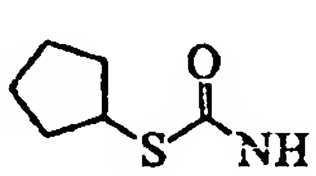
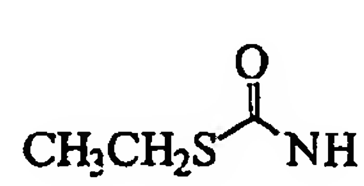
57. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2CH_3$, and R_8 is  ; and

58. R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2OCH_3$, and R_8 is  .

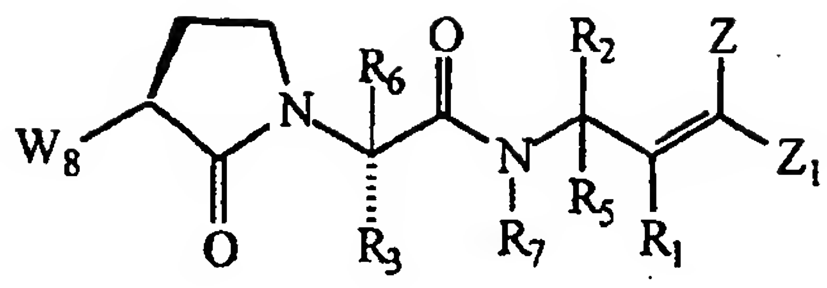
The invention also includes compounds **37** and **50-52** having the formula Ig:



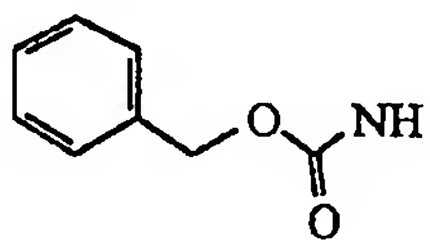
(Ig),

wherein R_1, R_3, R_5, R_7, W_5, W_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_7 is  in Compound 37, W_7 is  in Compound 50, W_7 is  in Compound 51, and W_7 is  in Compound 52.

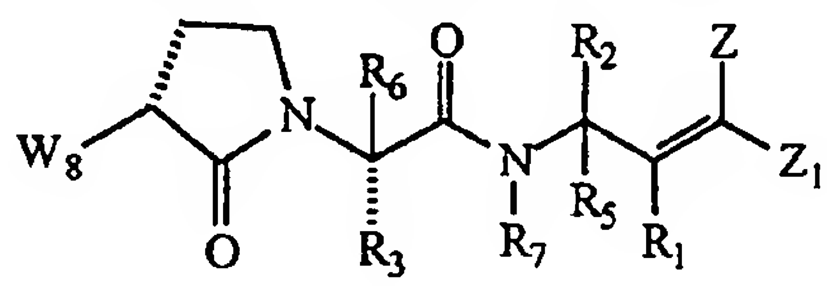
Compound **53** also corresponds to this invention. This compound has the formula Ih:



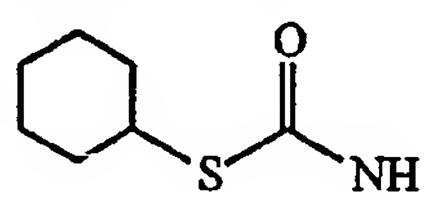
(Ih),

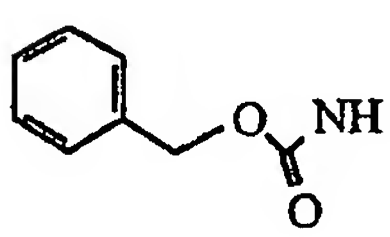
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and W_8 is  .

The invention also relates to compounds 54 and 55 having the formula (Ij):

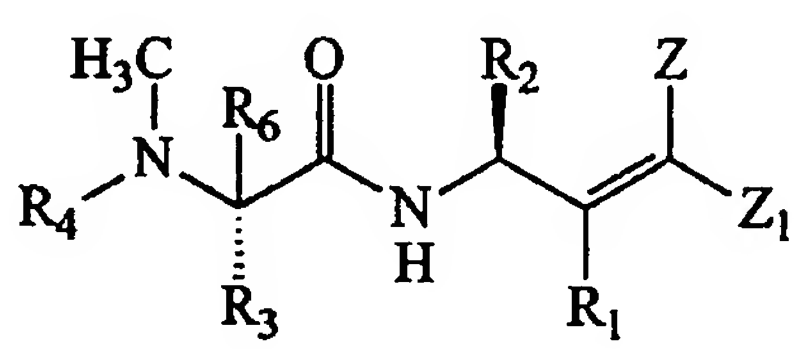


(Ij),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and W_8 is  in Compound 54, and W_8 is

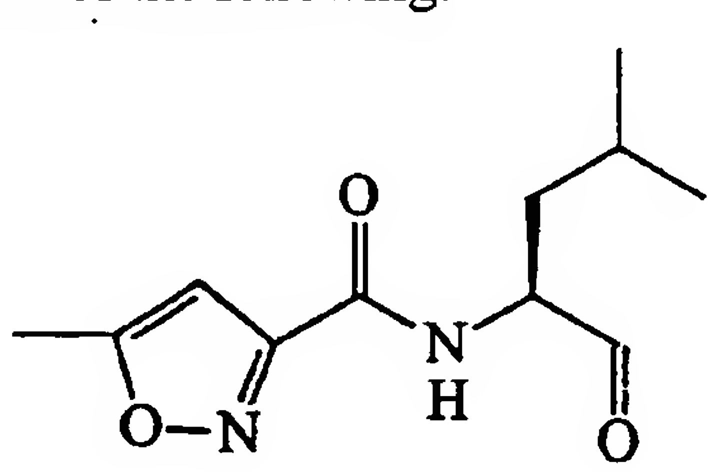
 in Compound 55.

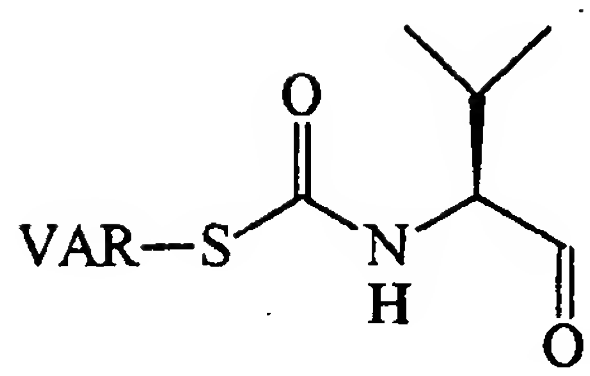
Other compounds according to the invention include the following compounds of formula X:

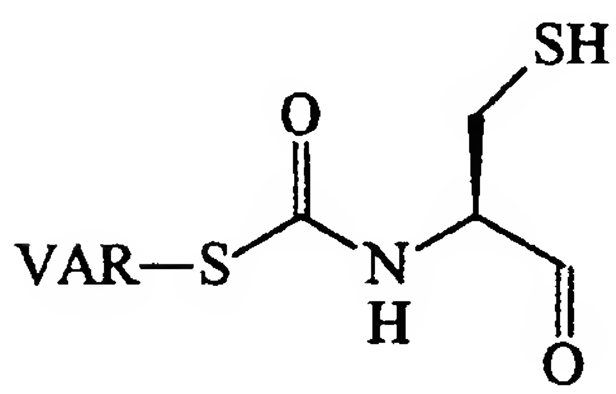


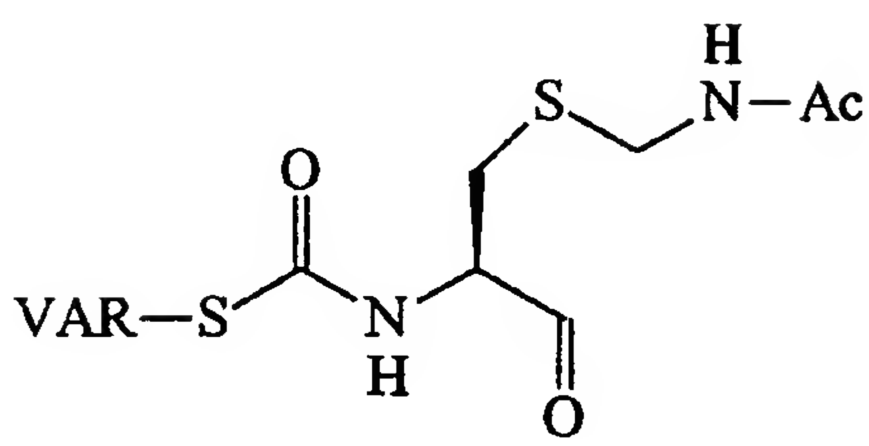
(X),

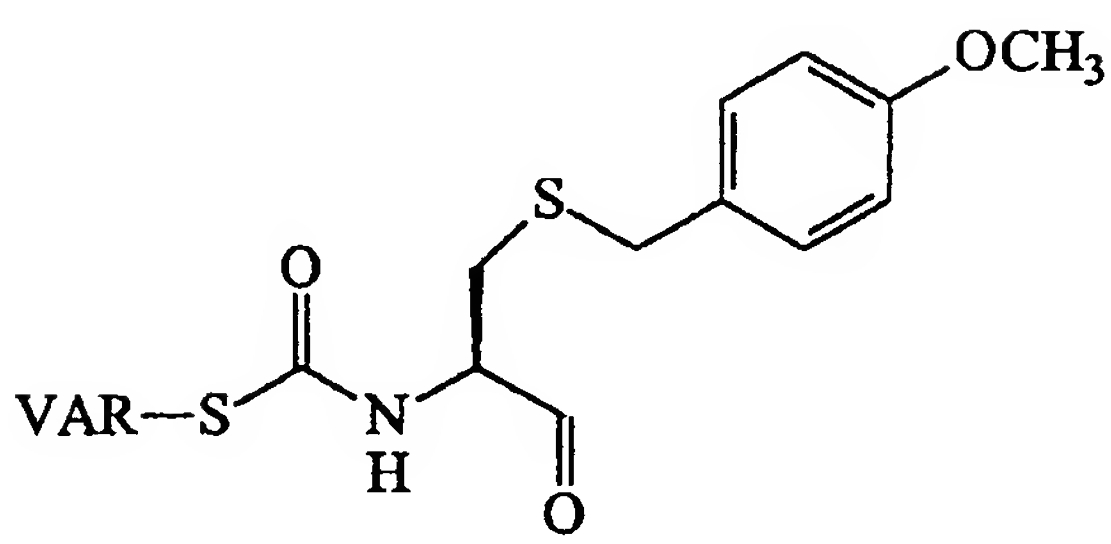
wherein R_1, R_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z_1 is $CO_2CH_2CH_3$, and R_4 is selected from one of the following:

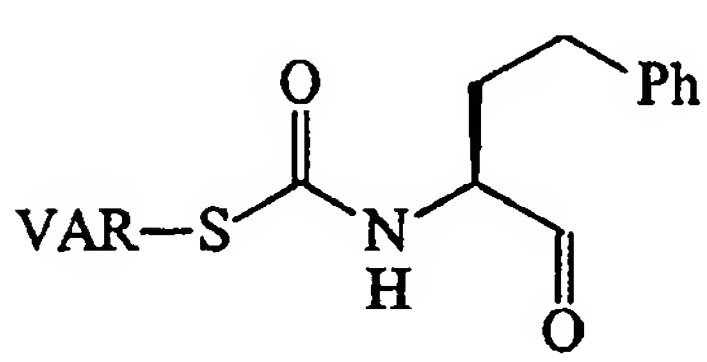
59 R_4 is  ;

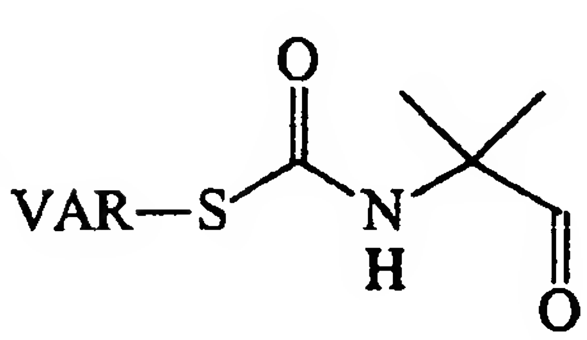
60. R_4 is  ;

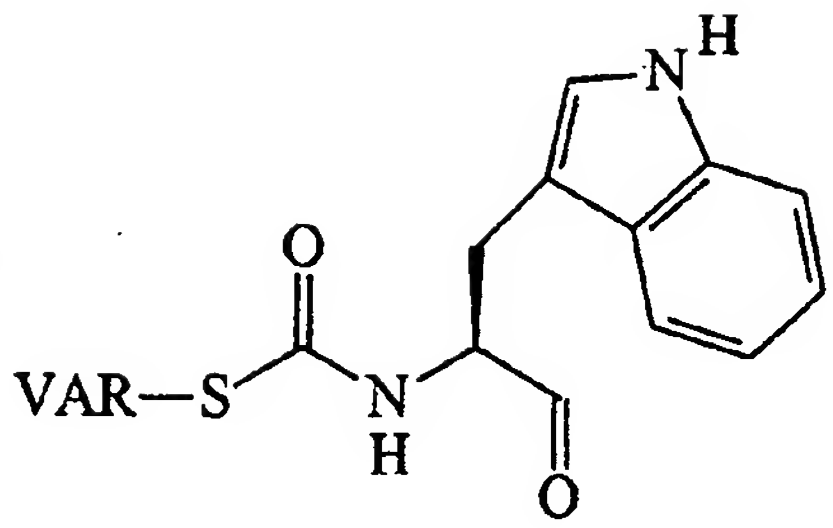
61. R_4 is  ;

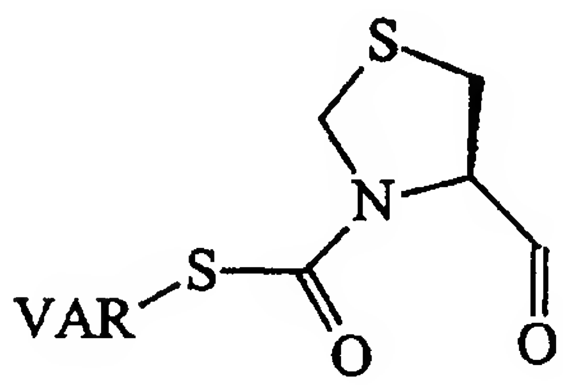
62. R_4 is  ;

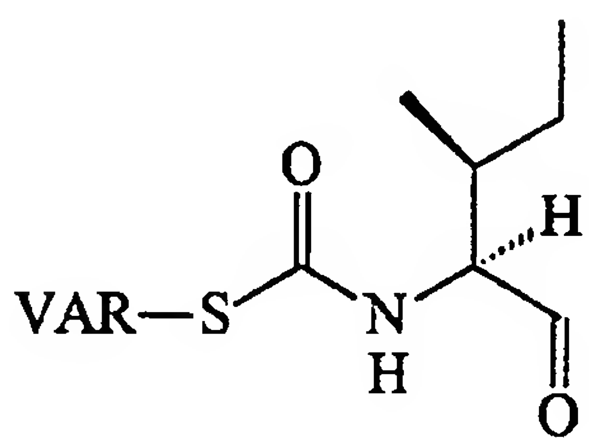
63. R_4 is  ;

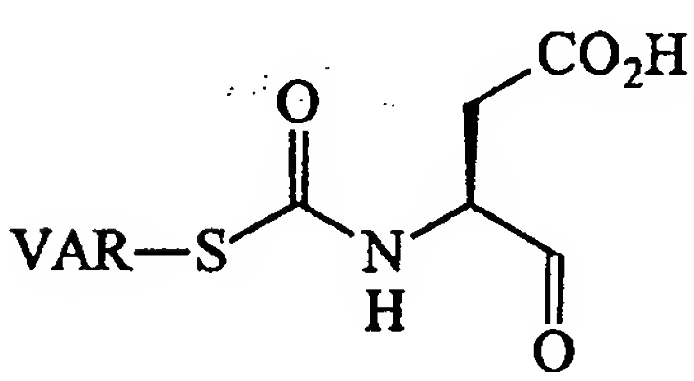
64. R_4 is  ;

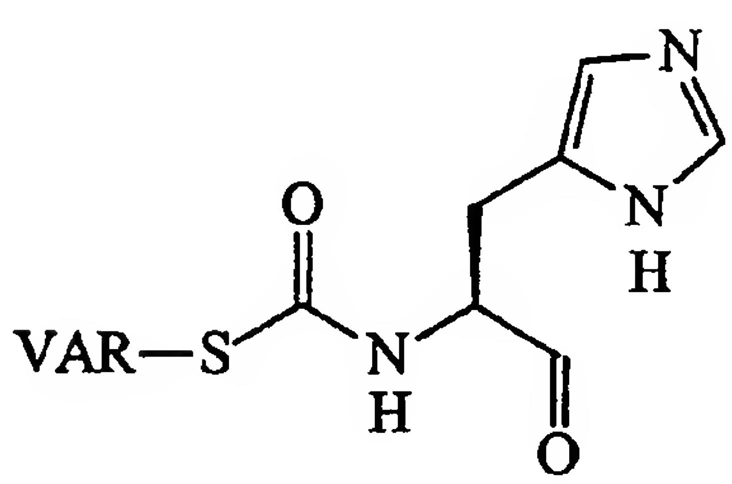
65. R_4 is  ;

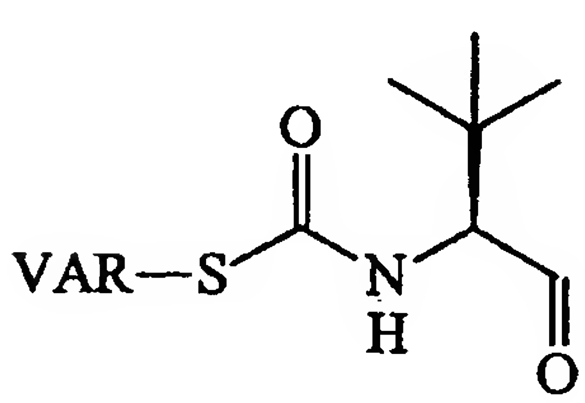
66. R_4 is  ;

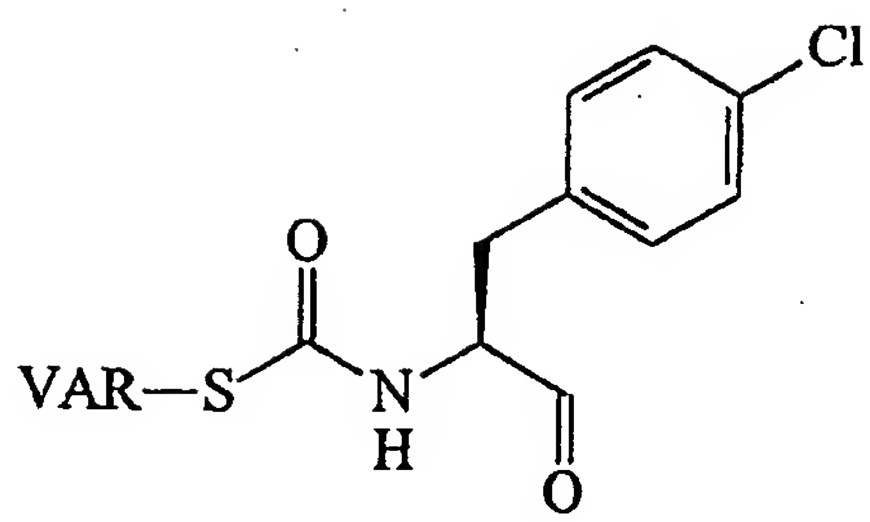
67. R_4 is  ;

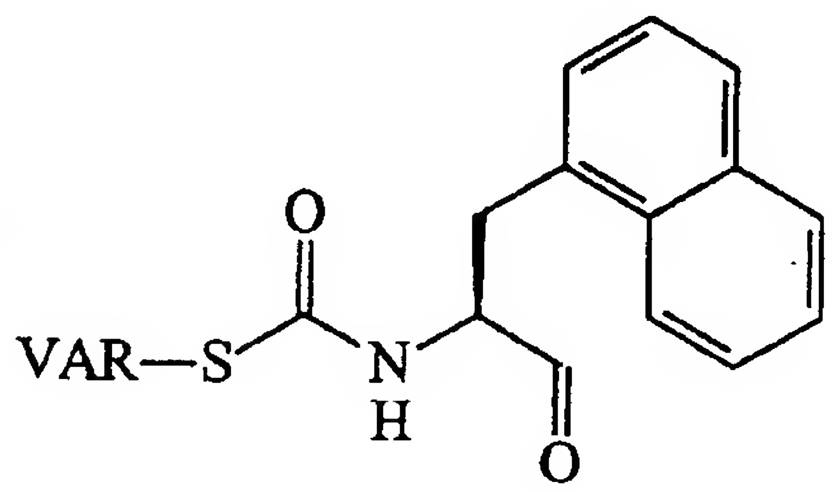
68. R_4 is  ;

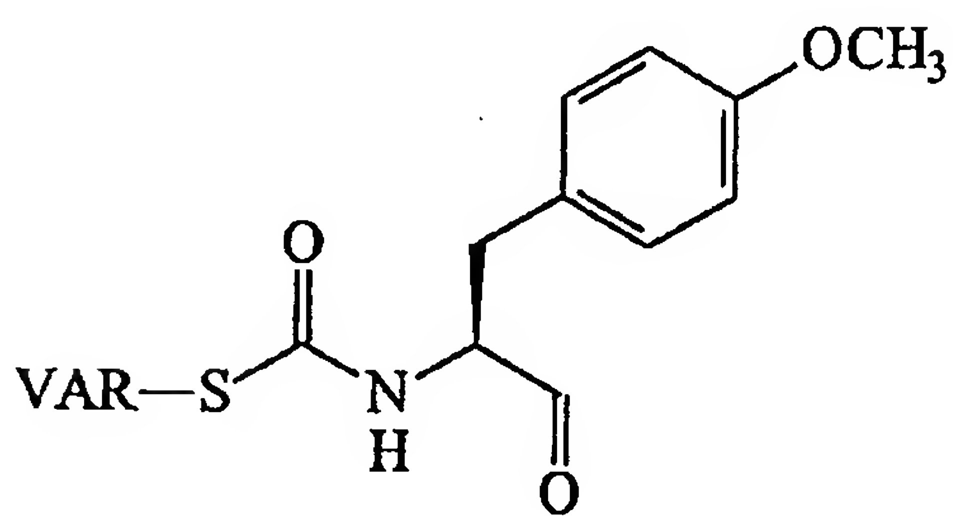
69. R_4 is  ;

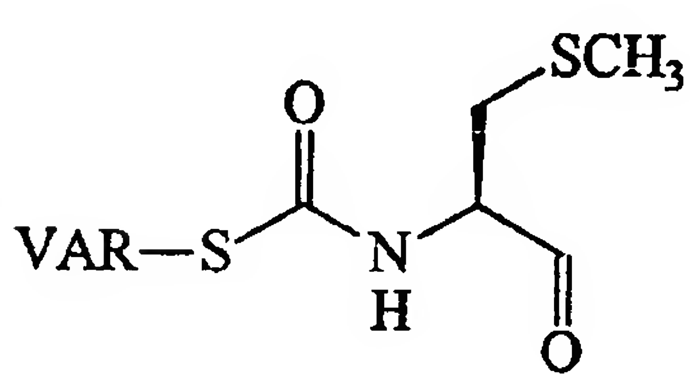
70. R_4 is  ;

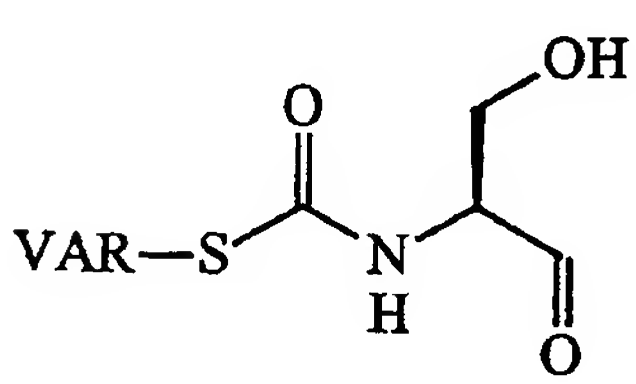
71. R_4 is  ;

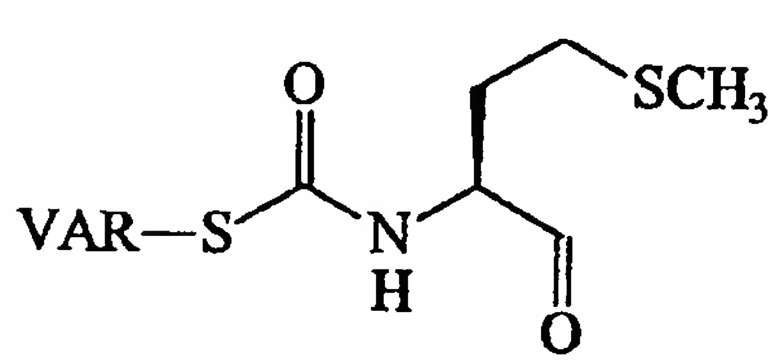
72. R_4 is  ;

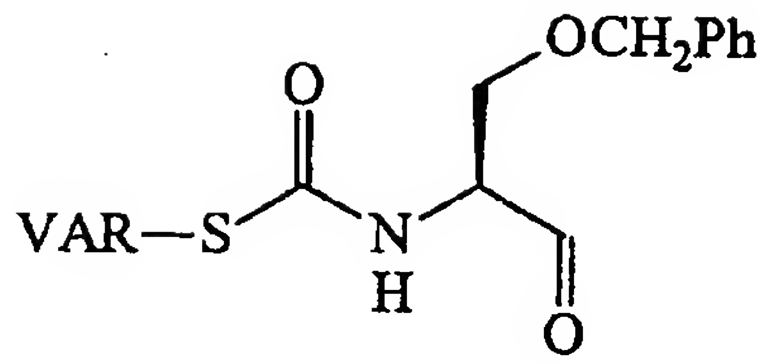
73. R_4 is  ;

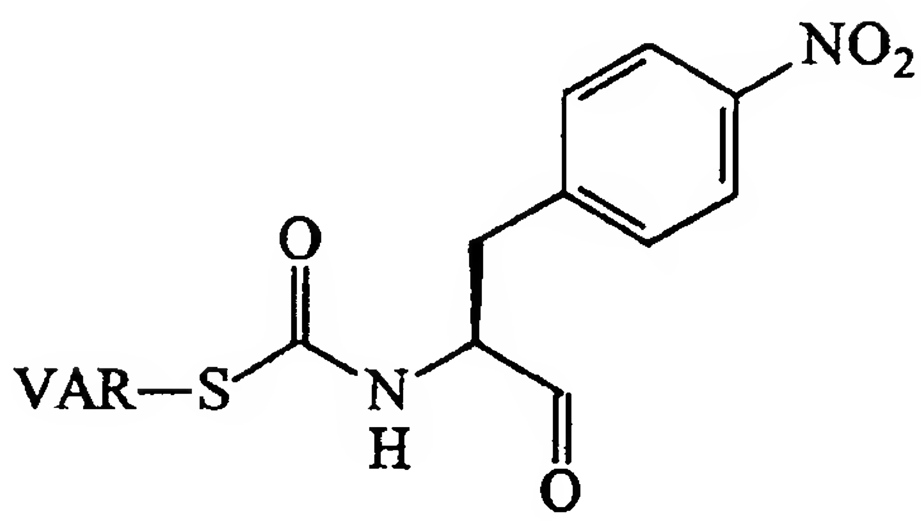
74. R_4 is  ;

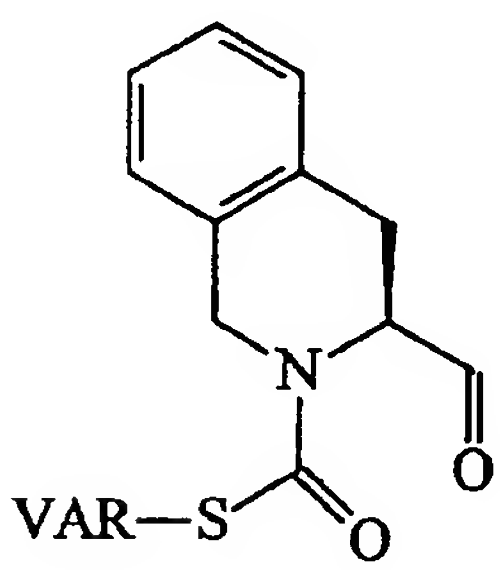
75. R_4 is  ;

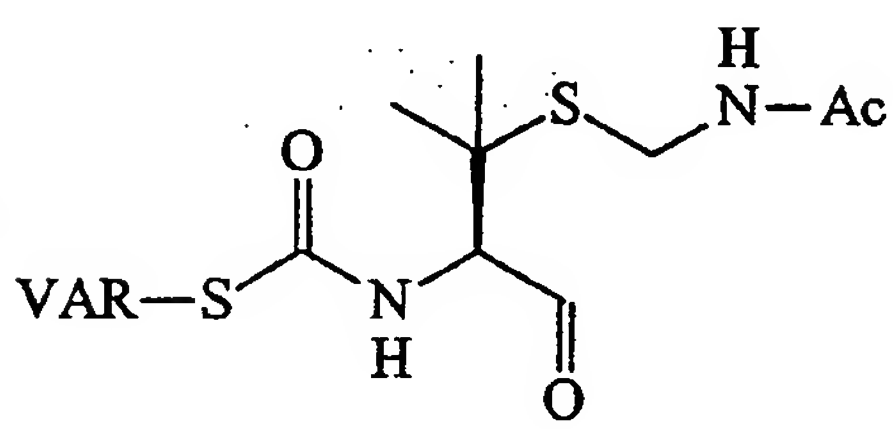
76. R_4 is  ;

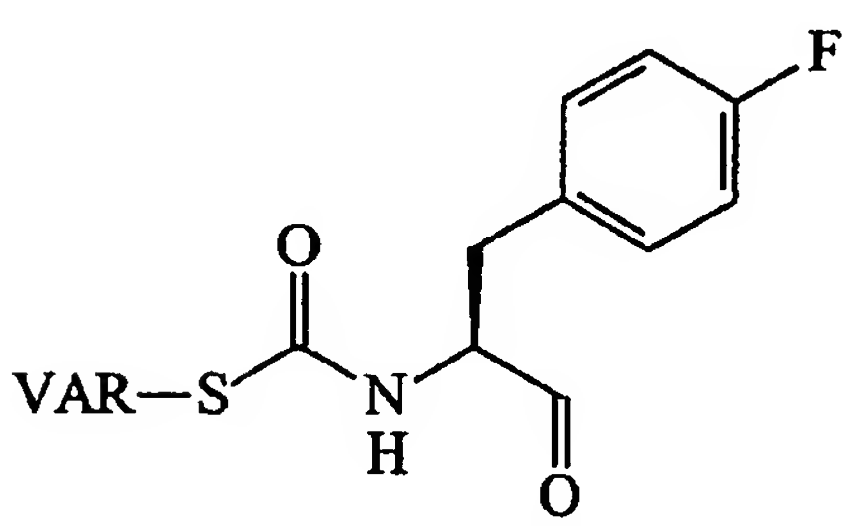
77. R_4 is  ;

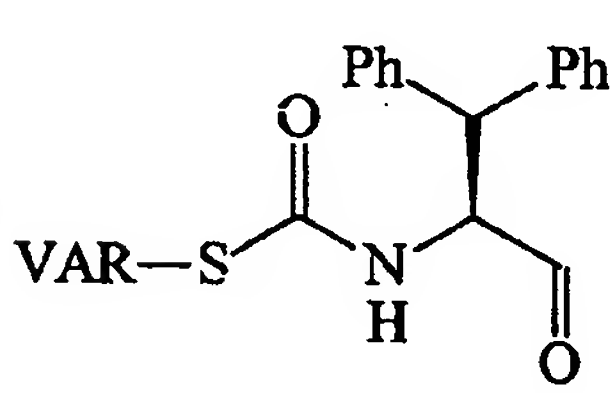
78. R_4 is  ;

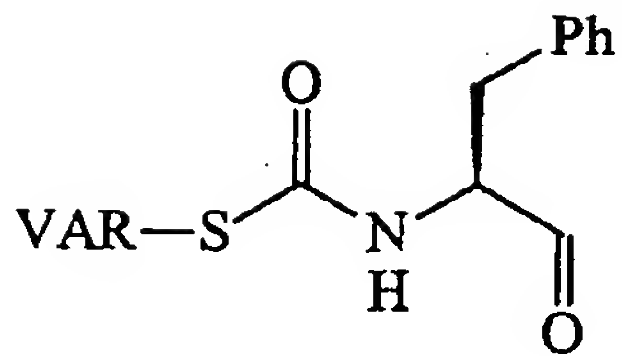
79. R_4 is  ;

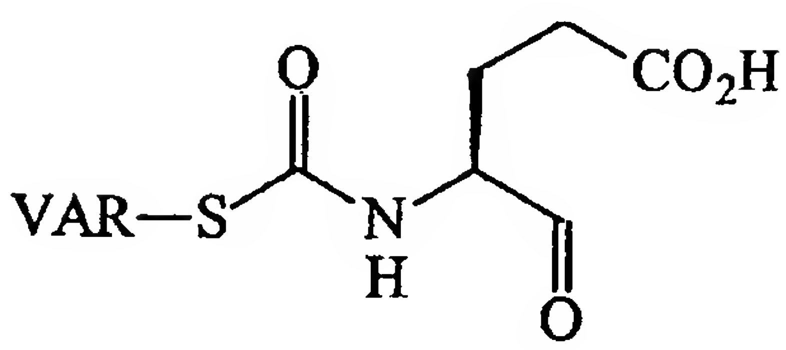
80. R_4 is  ;

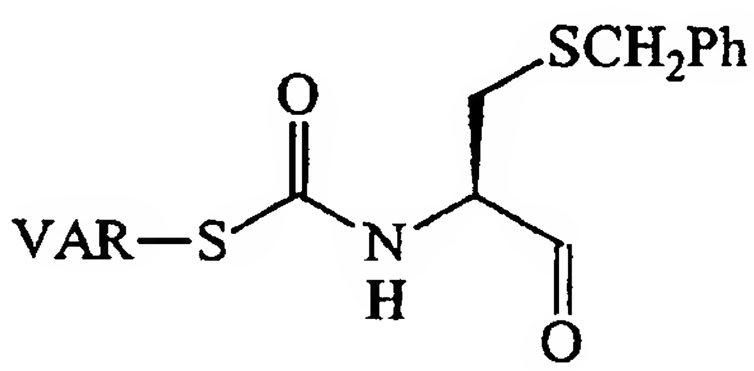
81. R_4 is  ;

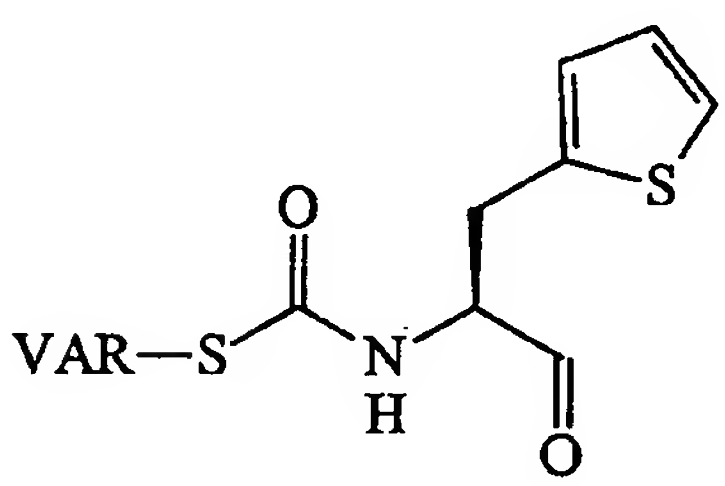
82. R_4 is  ;

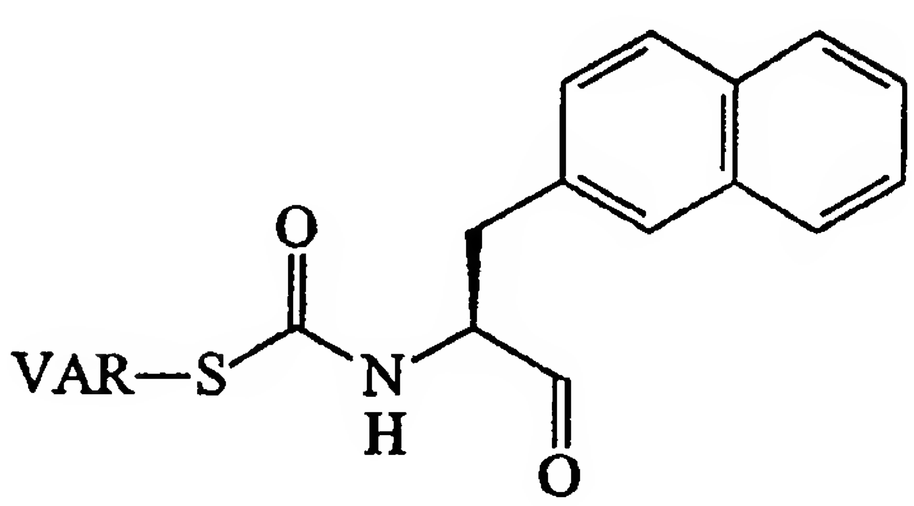
83. R_4 is  ;

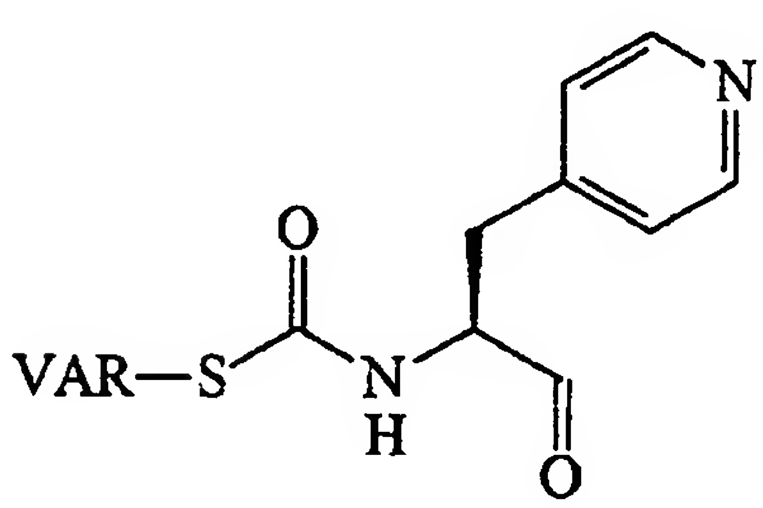
84. R_4 is  ;

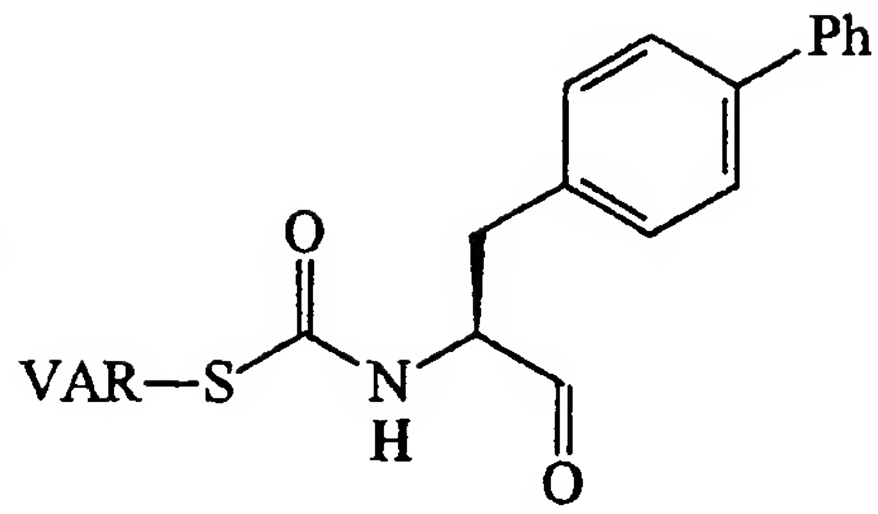
85. R_4 is  ;

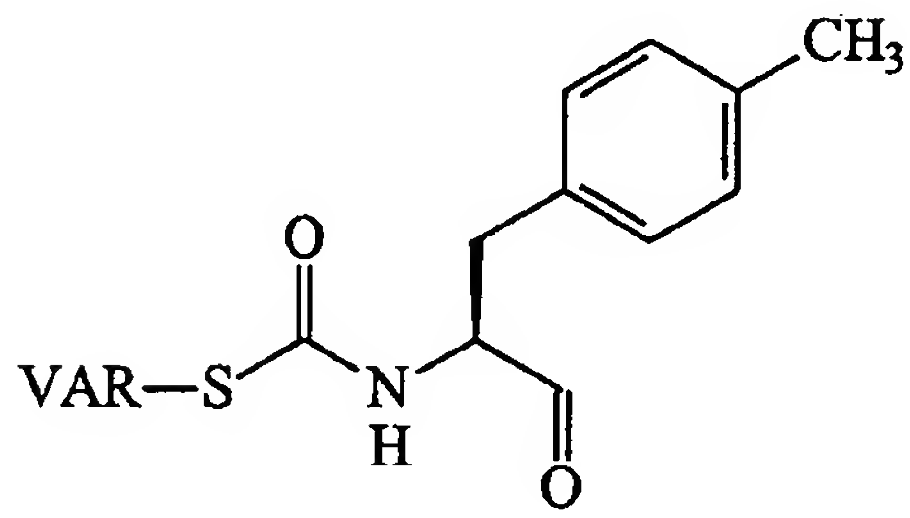
86. R_4 is  ;

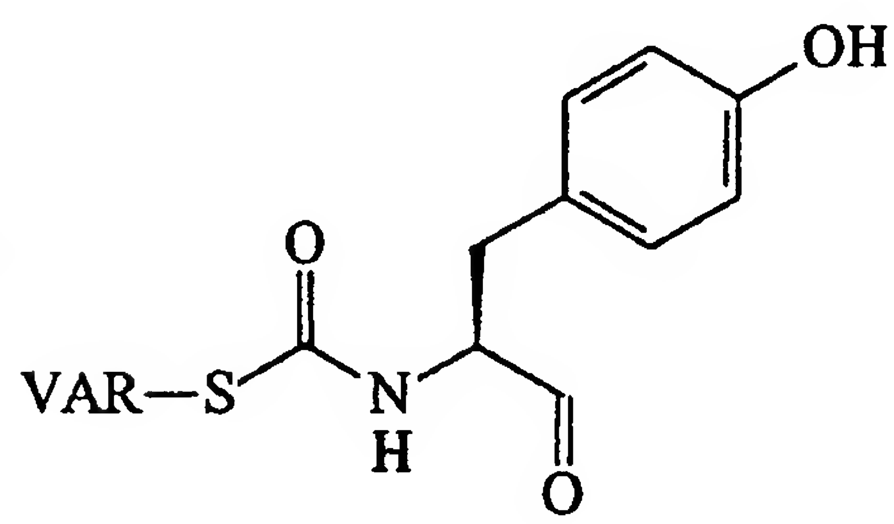
87. R_4 is  ;

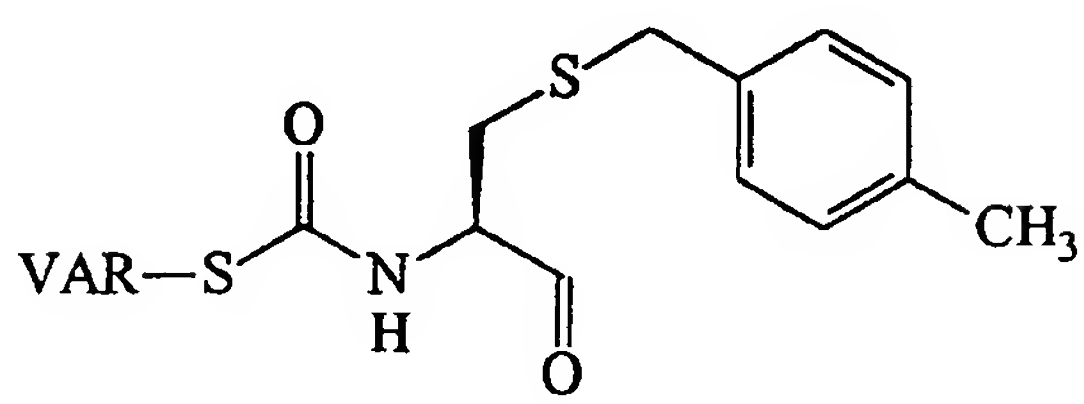
88. R_4 is  ;

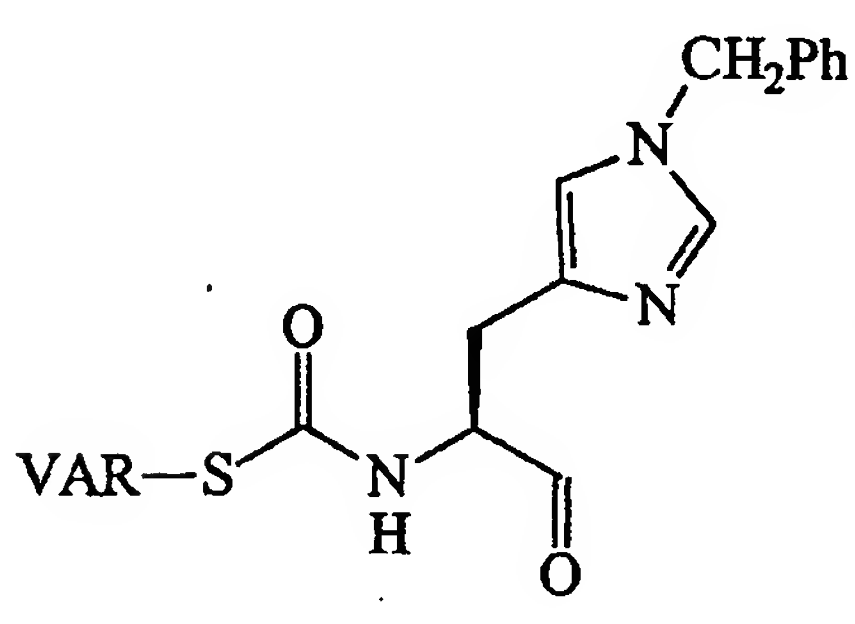
89. R_4 is  ;

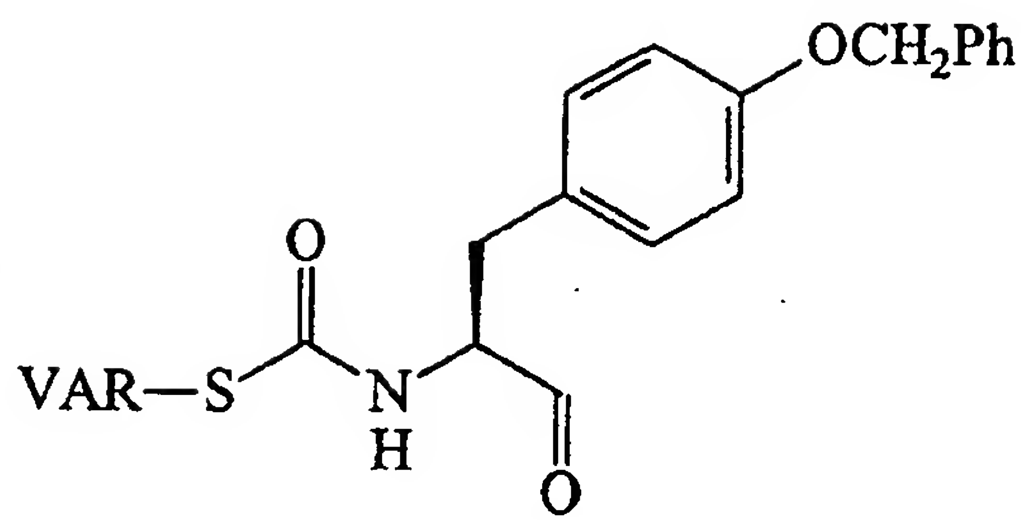
90. R_4 is  ;

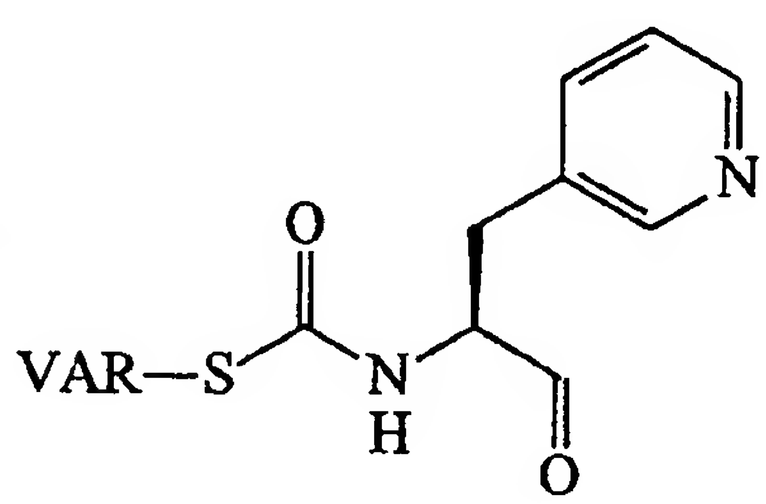
91. R_4 is  ;

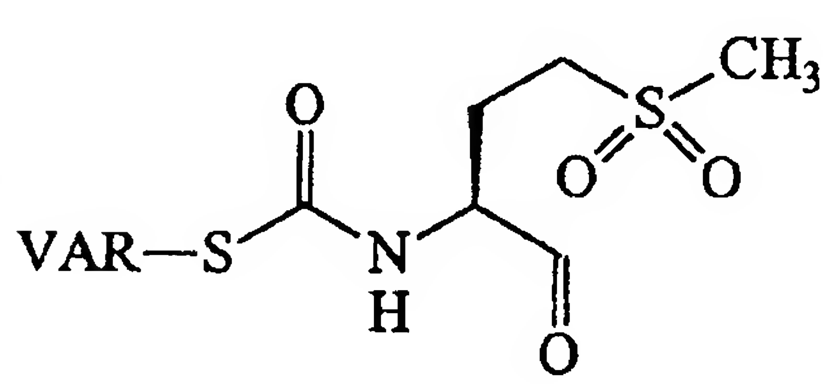
92. R_4 is  ;

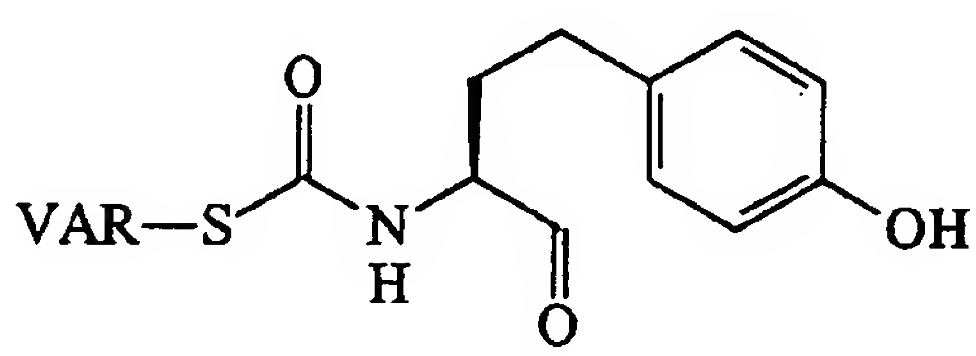
93. R_4 is  ;

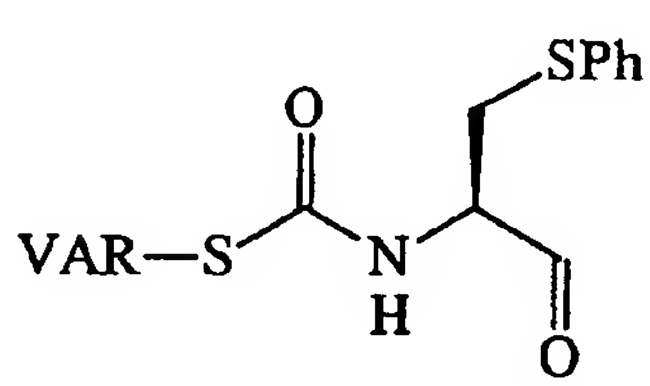
94. R_4 is  ;

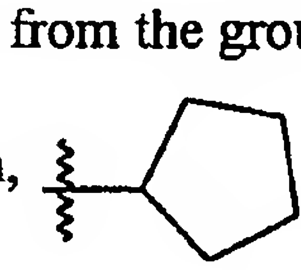
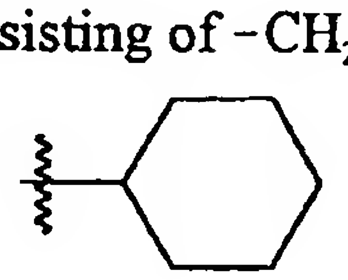
95. R_4 is  ;

96. R_4 is  ;

97. R_4 is  ;

98. R_4 is  ; and

99. R_4 is  ,

wherein VAR is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2Ph$, , and .

The present invention is further directed to methods of inhibiting picornaviral 3C protease activity that comprises contacting the protease for the purpose of such inhibition with an effective amount of a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof. For example, one can inhibit

picornaviral 3C protease activity in mammalian tissue by administering a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof. More particularly, the present invention is directed to methods of inhibiting rhinoviral protease activity.

The activity of the inventive compounds as inhibitors of picornaviral 3C protease activity may be measured by any of the methods available to those skilled in the art, including in vivo and in vitro assays. Examples of suitable assays for activity measurements include the Antiviral HI-HeLa Cell Culture Assay and the Normal Human Bronchial Epithelial Cell Assay, both described herein.

Administration of the compounds of formula I, or their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates, may be performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include, but are not limited to, oral, nasal, parenteral, topical, transdermal, and rectal.

The inventive compounds of formula I and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates, may be administered as a pharmaceutical composition in any suitable pharmaceutical form recognizable to the skilled artisan. Suitable pharmaceutical forms include, but are not limited to, solid, semisolid, liquid, or lyopholized formulations, such as tablets, powders, capsules, suppositories, suspensions, and aerosols. The pharmaceutical composition may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known to those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraural, and/or rectal administration.

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include

starch, lactose, calcium sulphate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers may include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged–release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g. solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of formula I or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof) and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of 3C protease activity, by any known method of administering the dose including topical, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

A "therapeutically effective amount" is intended to mean that amount of a compound of formula I that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus. The amount of a given compound of formula I that will correspond to a "therapeutically effective amount" will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, and the identity of the mammal in need thereof, but can nevertheless be readily determined by one of skill in the art.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus, and includes:

(a) prophylactic treatment in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but not yet diagnosed as having it;

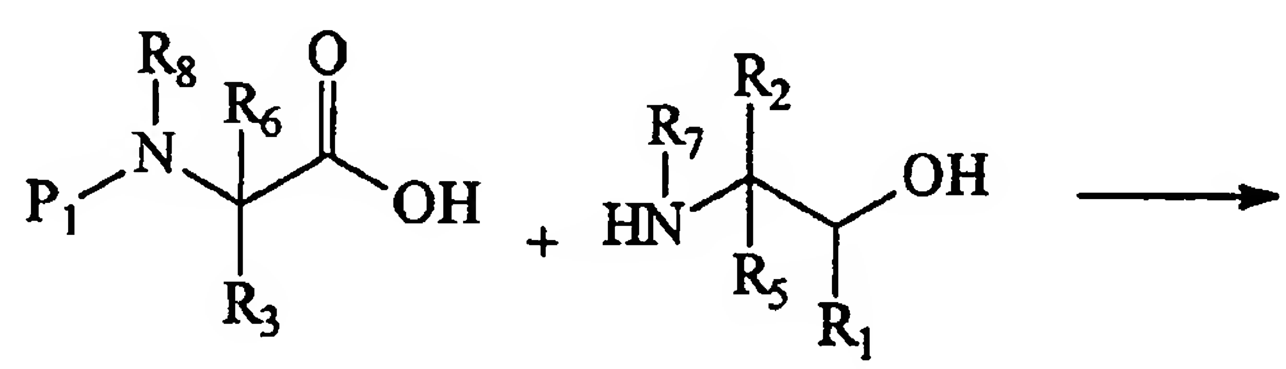
(b) inhibiting the disease condition; and/or

(c) alleviating, in whole or in part, the disease condition.

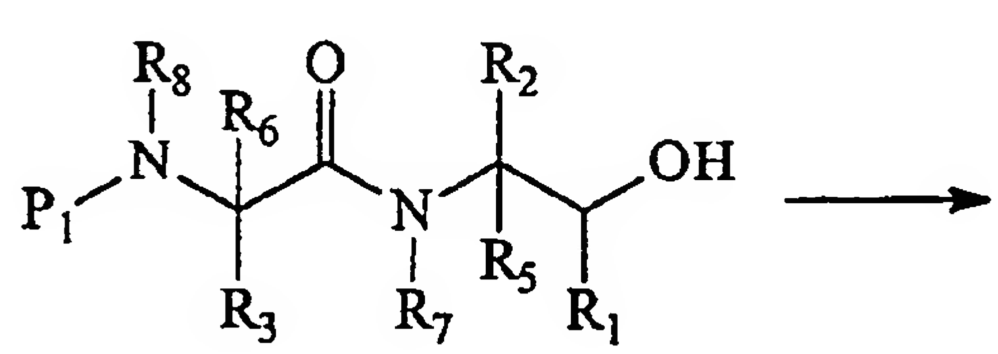
The inventive compounds, and their salts, solvates, crystal forms, active metabolites, and prodrugs, may be prepared by employing the techniques available in the art using starting materials that are readily available. Certain novel and exemplary methods of preparing the inventive compounds are described below.

Preferably, the inventive compounds of formula I are prepared by the novel methods of the present invention, including the four general methods shown below. In each of these general methods, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, Z, and Z_1 are as defined above (for formula I).

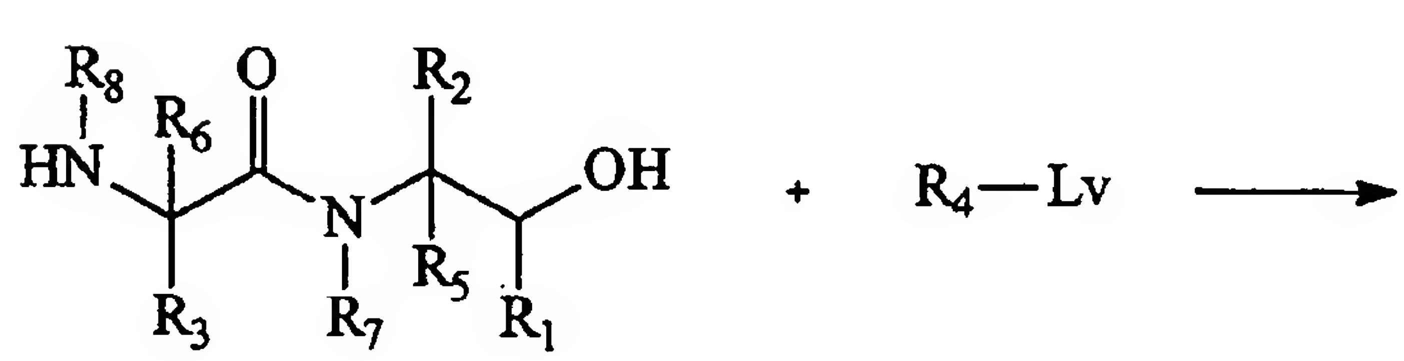
General Method I:



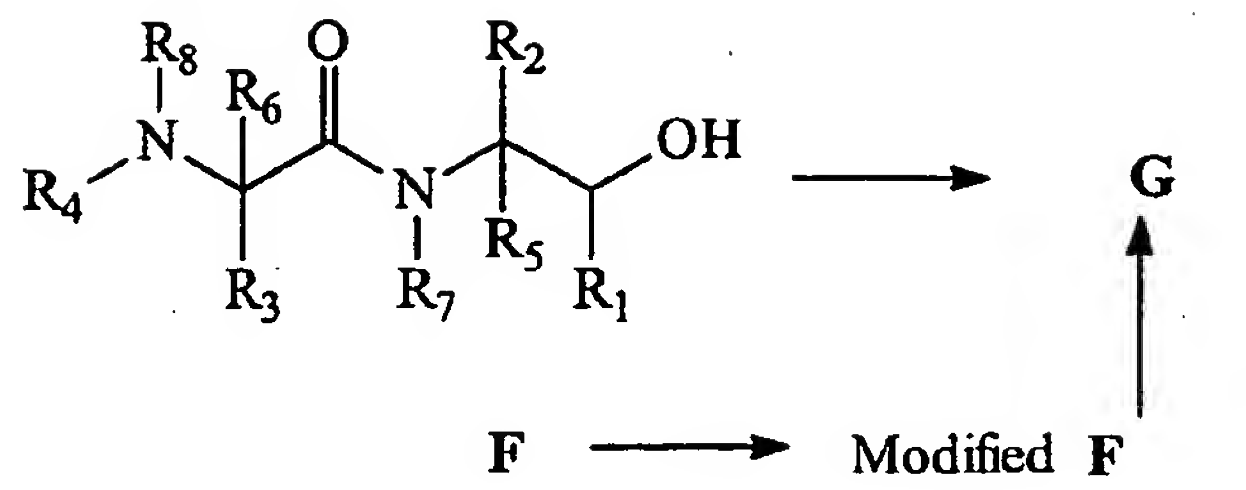
A B

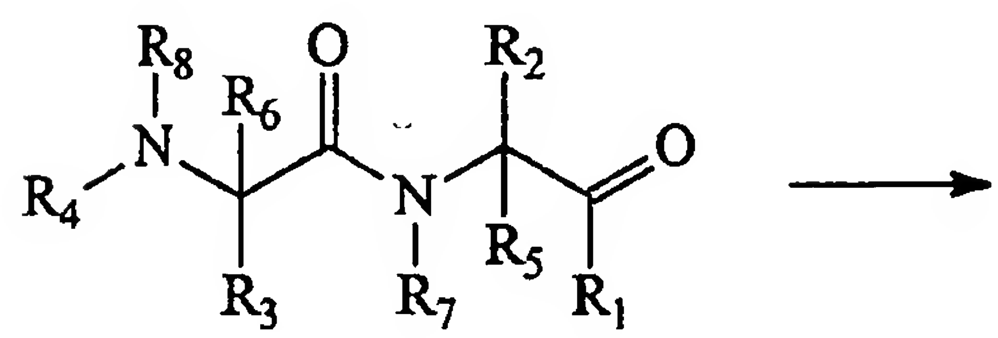


C

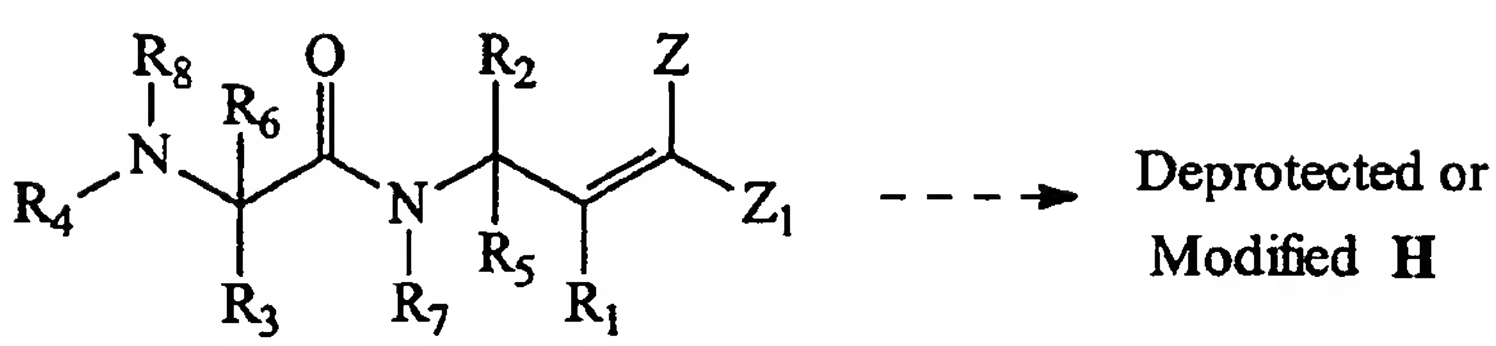


D E





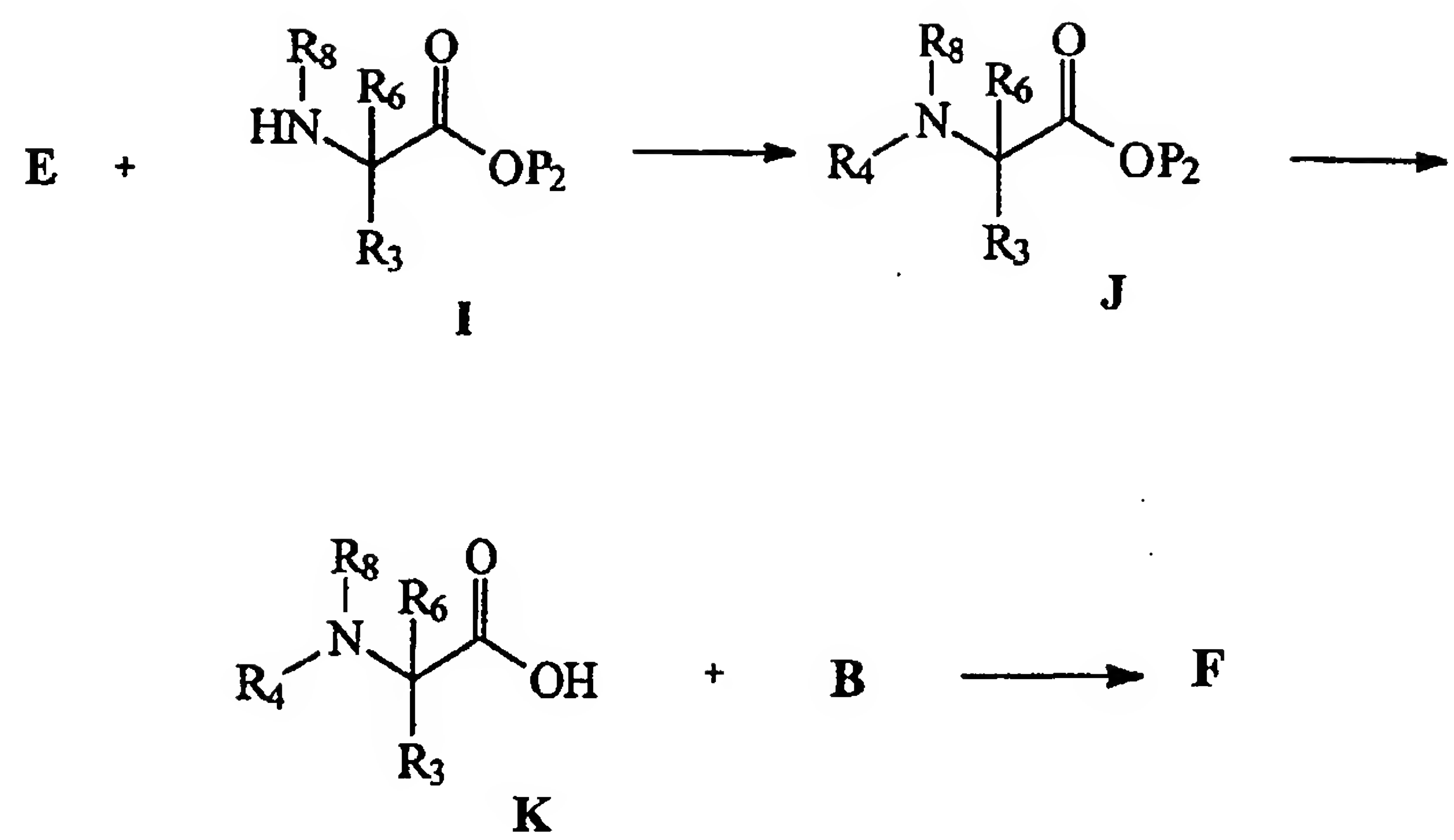
G



H

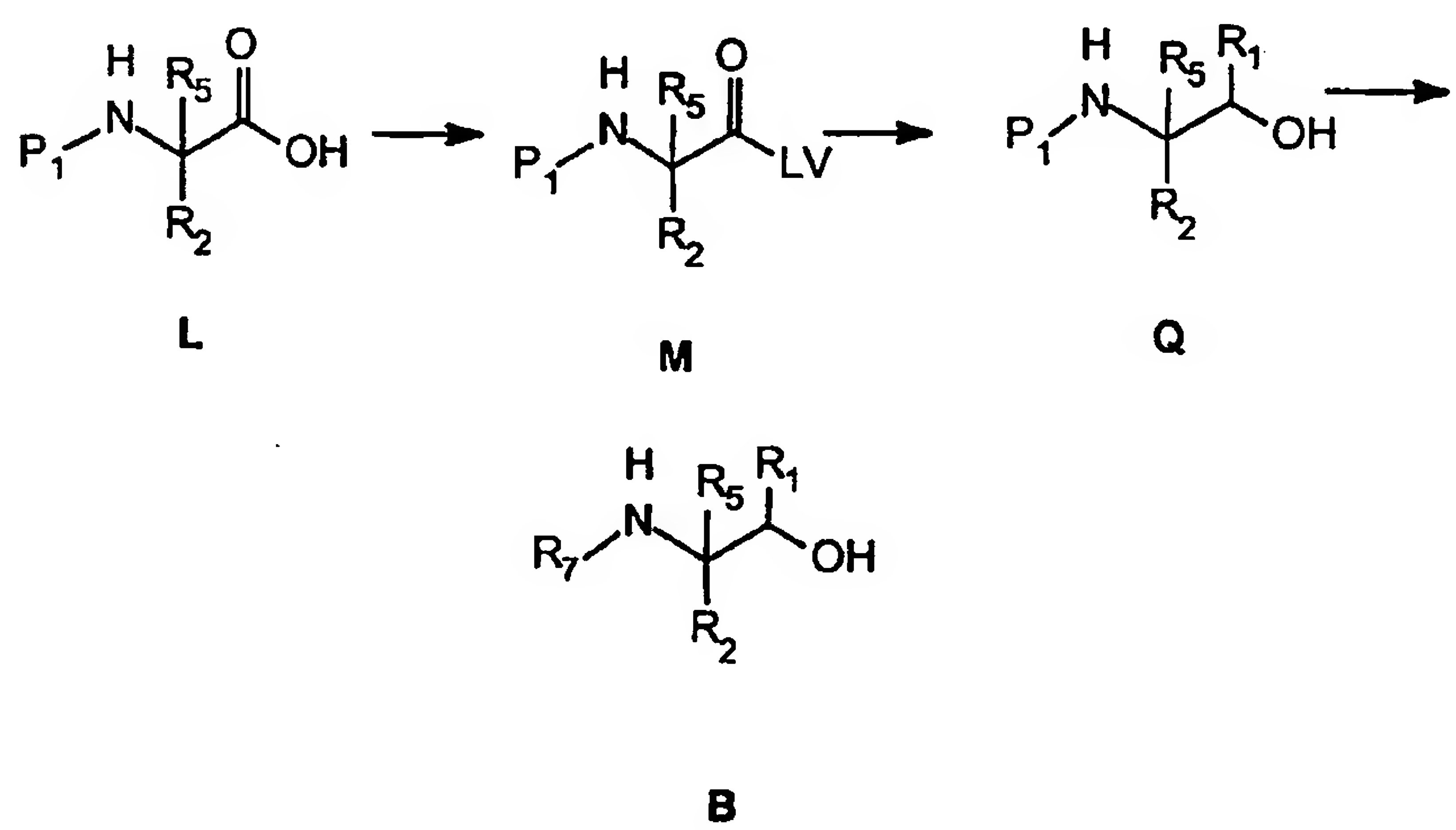
In General Method I, protected amino acid **A**, where P_1 is an appropriate protecting group for nitrogen, is subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to produce amide **C**. Amide **C** is then deprotected to give free amine (or salt thereof) **D**. Amine **D** and compound **E**, where "Lv" is an appropriate leaving group, are subjected to a bond forming reaction generating compound **F**. Compound **F** is oxidized to intermediate **G**, or modified at R_4 and/or R_8, to give one or more modified **F** compounds. Modified **F** compounds are oxidized to intermediate **G**. Intermediate **G** is then transformed into unsaturated product **H**. If protecting groups are used on any R groups (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

An alternative method to prepare intermediate **F** is described as follows:



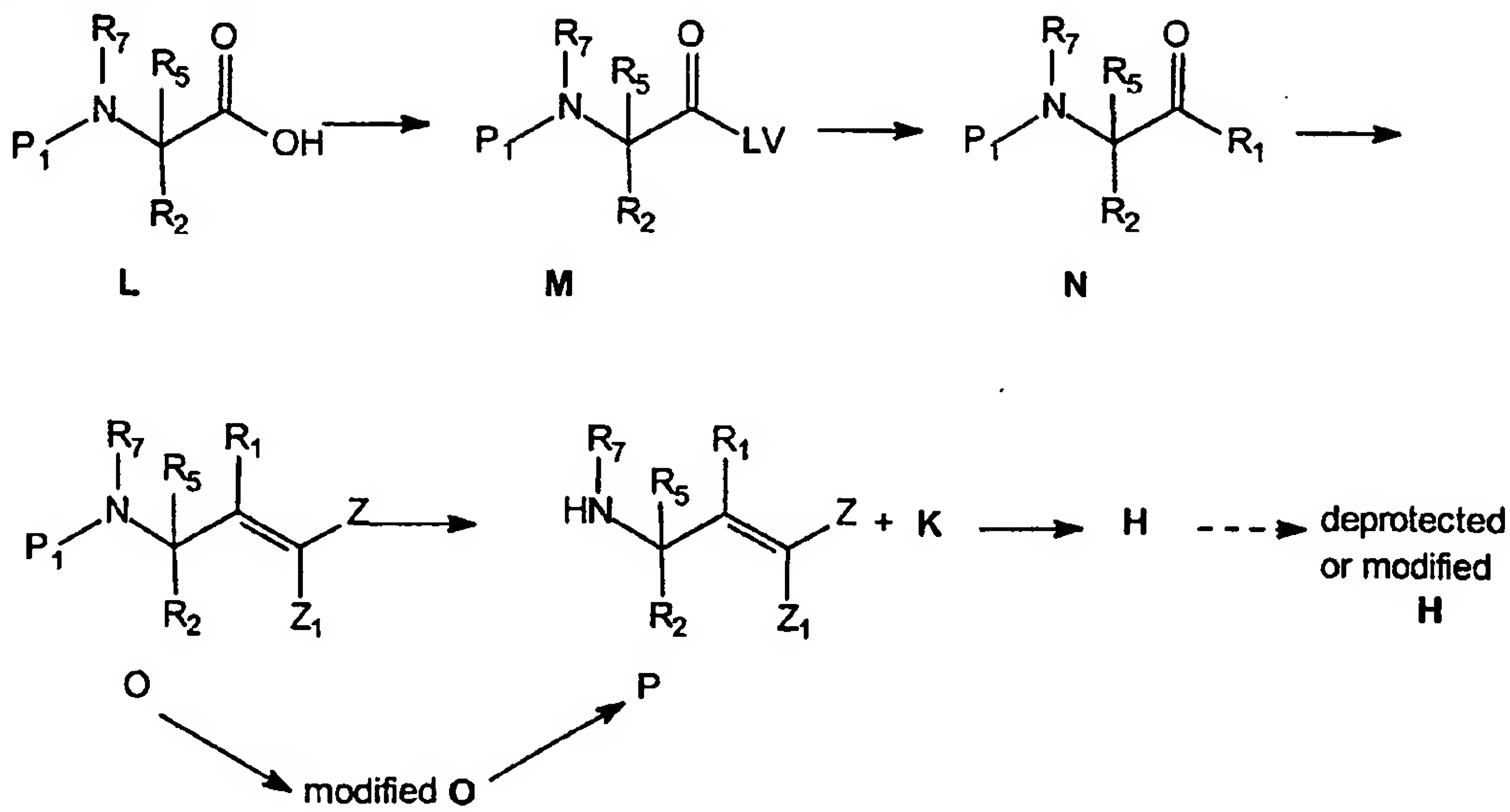
Compound **E** and amino acid (or salt thereof) **I**, where P_2 is an appropriate protecting group for oxygen, are subjected to a bond forming reaction to produce intermediate **J**. Intermediate **J** is deprotected to yield free carboxylic acid **K**, which is subsequently subjected to an amide forming reaction with amino alcohol (or salt thereof) **B** to generate intermediate **F**.

Amino alcohol **B** can be prepared as follows:



Amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to carbonyl derivative **M**, where "Lv" is a leaving group. Compound **M** is subjected to a reaction where "Lv" is reduced to protected amino alcohol **Q**. Amino alcohol **Q** is deprotected to give amino alcohol **B**.

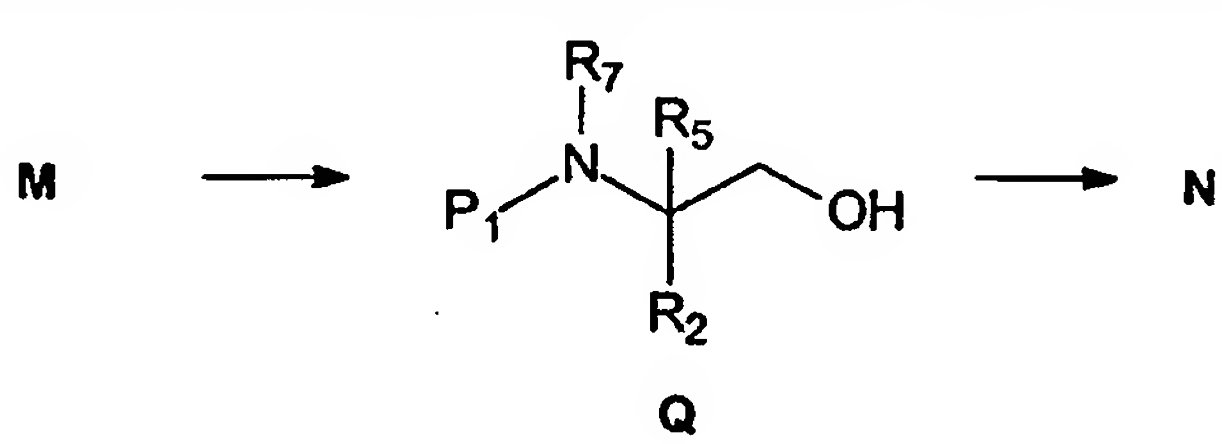
General Method **II**:



In General Method **II**, amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative **M**, where "Lv" is a leaving group. Compound **M** is subjected to a reaction where "Lv" is replaced by R_1 to give derivative **N**. Derivative **N** is then transformed into unsaturated product **O**. Unsaturated compound **O** is deprotected to give free amine (or salt thereof) **P**, or modified one or more times at R_2, R_5, R_7, Z, and/or Z_1 to give one or more modified **O** compounds.

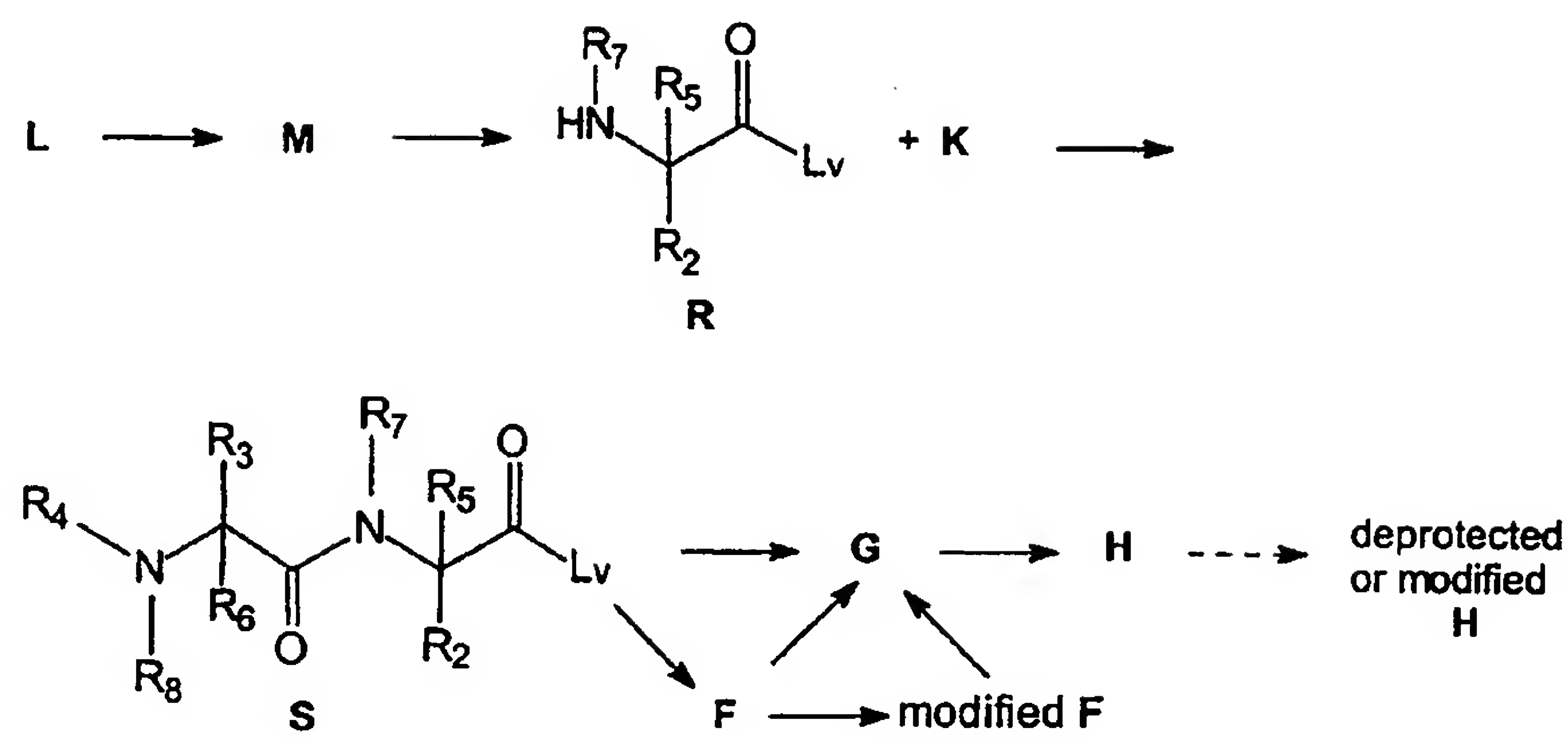
Modified **O** is then deprotected to give amine (or salt thereof) **P**. Amine **P** is subsequently subjected to an amide forming reaction with carboxylic acid **K**, prepared as described in General Method **I**, to give final product **H**. If protecting groups were used on any R group (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

An alternative method to prepare intermediate **N** is described as follows:



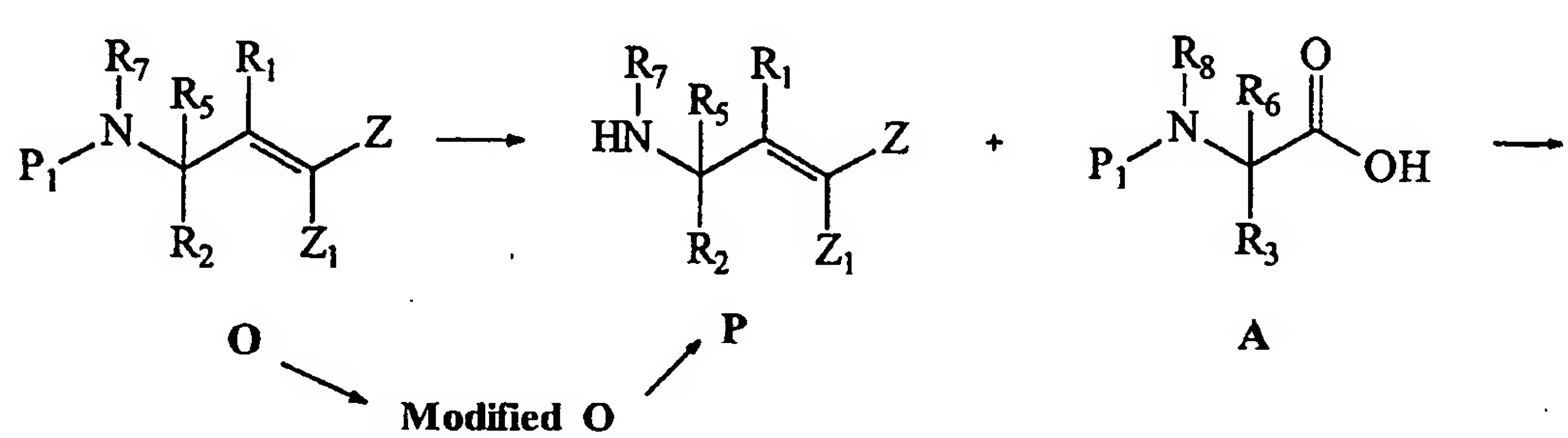
Compound **M** is subjected to a reaction where "Lv" is reduced to protected amino alcohol **Q**. Amino alcohol **Q** is subsequently oxidized to derivative **N**.

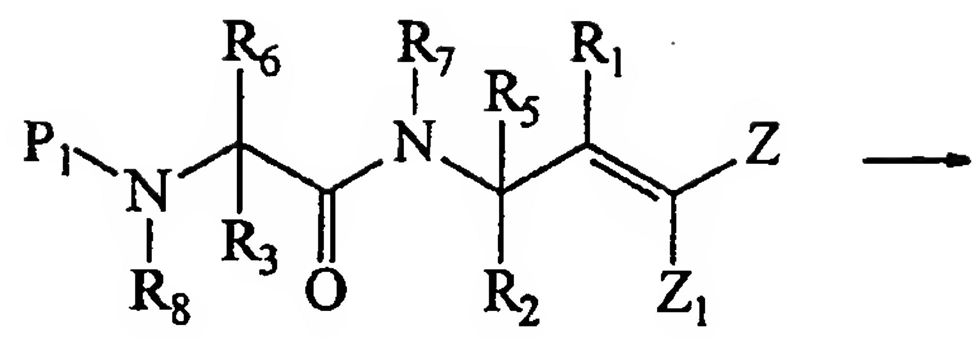
General Method **III**:



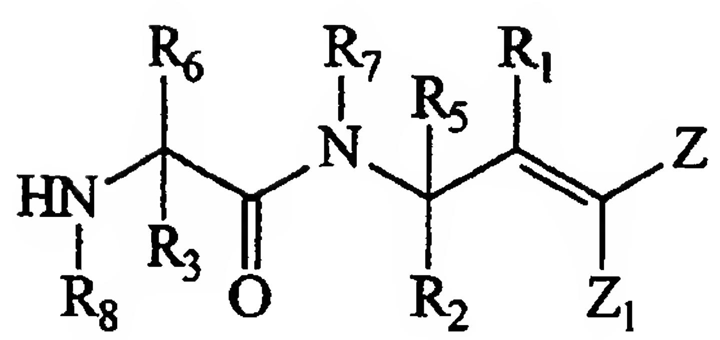
In General Method **III**, amino acid **L**, where P_1 is an appropriate protecting group for nitrogen, is converted to a carbonyl derivative **M**, where "Lv" is a leaving group. Derivative **M** is deprotected to give free amine (or salt thereof) **R**, which subsequently is subjected to an amide forming reaction with carboxylic acid **K** to give intermediate **S**. Intermediate S is then either converted directly to carbonyl intermediate **G**, or successively reduced to alcohol **F**, which is then oxidized to **G**. Intermediate **G** is subjected to a reaction to yield the unsaturated final product **H**. If protecting groups were used on any R groups (R_1–R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

General Method **IV**:





T

 + R_4—Lv

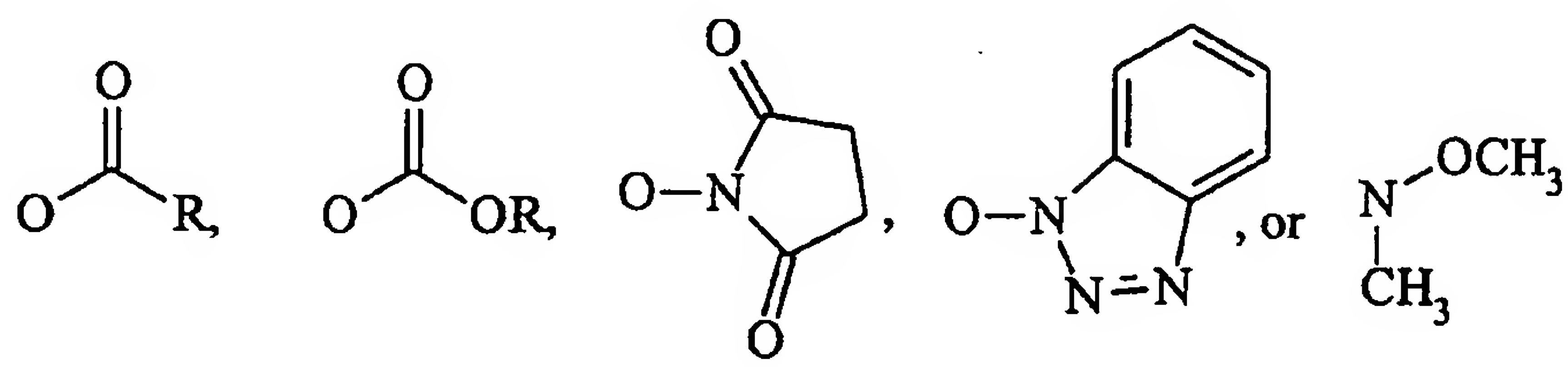
U **E**

⟶ **H** - - - → **Deprotected or Modified H**

In General Method **IV**, free amine (or salt thereof) **P**, prepared from intermediate **O** as described in General Method **II**, is converted to amide **T** by reaction with amino acid **A**, where P_1 is an appropriate protecting group for nitrogen. Compound **T** is further deprotected to free amine (or salt thereof) **U**, which is subsequently converted to **H** with reactive intermediate **E**. If protecting groups were used on any R groups (R_1-R_8) and/or on Z and/or Z_1, product **H** is deprotected and/or further modified to yield "deprotected or modified **H**."

Suitable protecting groups for nitrogen are recognizable to those skilled in the art and include, but are not limited to benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, p-methoxybenxyloxycarbonyl, trifluoroacetamide, and p-toluenesulfonyl. Suitable protecting groups for oxygen are recognizable to those skilled in the art and include, but are not limited to $-CH_3$, $-CH_2CH_3$, tBu, $-CH_2Ph$, $-CH_2CH{=}CH_2$, $-CH_2OCH_2CH_2Si(CH_3)_3$, and $-CH_2CCl_3$. Other examples of suitable protecting groups for nitrogen or oxygen can be found in T. Green & P. Wuts, Protective Groups in Organic Synthesis (2nd ed. 1991), which is incorporated herein by reference.

Suitable leaving groups are recognizable to those skilled in the art and include, but are not limited to, Cl, Br, I, sulfonates, O-alkyl groups,



wherein "R" is any suitable substituent, such as an alkyl group or an aryl group. Other examples of suitable leaving groups are described in J. March, Advanced Organic Chemistry, Reactions, Mechanisms, and Structure (4th ed. 1992) at pages 205, 351-56, 642-43, 647, 652-53, 666, 501, 520-21, 569, 579-80, 992-94, 999-1000, 1005, and 1008, which are incorporated herein by reference.

EXAMPLES

Proton magnetic resonance spectra (NMR) were determined using a Tech-Mag spectrometer operating at a field strength of 300 megahertz (MHZ) or Varian UNITY*plus* 300. Chemical shifts are reported in parts per million (δ) and setting the references such that in $CDCl_3$ the $CHCl_3$ is at 7.26 ppm, in CD_3OD the CH_3OH is at 4.9 ppm, in C_6D_6 the C_6H_6 is at 7.16 ppm, in acetone-d_6 the acetone is at 2.02 ppm, and in DMSO-d_6 the DMSO is at 2.49 ppm. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; bs, broad singlet; bt, broad triplet; m, multiplet. Mass spectra (FAB; fast atom bombardment) were determined at the Scripps Research Institute Mass Spectometry Facility, San Diego, CA. Infrared absorption (IR) spectra were taken on a MIDAC Corporation FTIR or a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc. Norcross, Georgia and gave results for the elements stated with ± 0.4% of the theoretical values. Flash chromatography was performed using Silica gel 60 (Merck Art 9385). Thin layer chromatographs ("TLC") were performed on precoated sheets of silica 60 F_{254} (Merck Art 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Anhydrous *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethysulfoxide

(DMSO), were used as is. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. "Et_2O" refers to diethyl ether. "Pet. ether" refers to petroleum ether with a boiling range of 36-53 °C. "TFA" refers to trifluoroacetic acid. "Et_3N" refers to triethylamine. Other abbreviations include: methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), acetyl (Ac), methyl (Me), triphenylmethyl (Tr), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (BOC), *m*-chloroperoxybenzoic acid (*m*-CPBA), alanine (Ala), glutamine (Gln), proline (Pro), leucine (Leu), methionine (Met), phenylalanine (Phe), and homophenylalanine (hPhe), where "L" represents natural amino acids and "D" unnatural amino acids. "DL" represents racemic mixtures. A simplified naming system was used to identify intermediates and final products: Amino acid and peptide alcohols are given the suffix 'ol' (for example "methionol"). Amino acid and peptide aldehydes are given the suffix 'al' (for example "methional"). When naming final products, italicized amino acid abbreviations represent modifications at the C-terminus of that residue where the following apply:

1. acrylic acid esters are reported as either "E" (trans) or "Z" (cis) propenoates.
2. lactones 6, 8, 10, and 12 are reported as E-α-vinyl-γ-butyrolactones.
3. acrylamides are reported as either E or Z propenamides except in the case of compound 7, which is reported as 1-(2',3'-Dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone and compound 26, which is reported as 1-[1',2'-oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)- E-propenone.
4. acryloxazolidone 17 is reported as 1-[2'-oxazolidon-3'-yl]-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-propenone.

Example 1 - Preparation of Compound 1: Ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate BOC-L-(Tr-Gln)-N(OMe)Me.

Isobutyl chloroformate (4.77 mL, 36.8 mmol, 1.0 equiv) was added to a solution of BOC-L-(Tr-Gln) (18.7 g, 36.7 mmol, 1 equiv) and 4-methylmorpholine (8.08 mL, 73.5 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, then *N,O*-dimethylhydroxylamine hydrochloride (3.60 g, 36.7 mmol, 1.0 equiv) was added. The resulting solution was stirred at 0 °C for 20 min and at 23 °C for 2 h, and

then it was partitioned between water (150 mL) and CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (gradient elution, 20-40% hexanes in EtOAc) provided BOC-L-(Tr-Gln)-N(OMe)Me (16.1 g, 82%) as a white foam: IR (KBr) 3411, 3329, 3062, 1701, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.63-1.77 (m, 1 H), 2.06-2.17 (m, 1 H), 2.29-2.43 (m, 2 H), 3.17 (s, 3 H), 3.64 (s, 3 H), 4.73 (s, bs, 1 H), 5.38-5.41 (m, 1 H), 7.20-7.31 (m, 15 H); Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

Preparation of Intermediate BOC-L-(Tr-Glutaminal).

Diisobutylaluminum hydride (50.5 mL of a 1.5 M solution in toluene, 75.8 mmol, 2.5 equiv) was added to a solution of [BOC-L-(Tr-Gln)]-N(OMe)Me (16.1 g, 30.3 mmol, 1 equiv) in THF at -78 °C, and the reaction mixture was stirred at -78 °C for 4 h. Methanol (4 mL) and 1.0 M HCl (10 mL) were added sequentially, and the mixture was warmed to 23 °C. The resulting suspension was diluted with Et_2O (150 mL) and was washed with 1.0 M HCl (3 x 100 mL), half-saturated $NaHCO_3$ (100 mL), and water (100 mL). The organic layer was dried over $MgSO_4$, filtered, and was concentrated to give crude BOC-L-(Tr-Glutaminal) (13.8 g, 97%) as a white solid: mp = 114-116 °C; IR (KBr) 3313, 1697, 1494 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.65-1.75 (m, 1 H), 2.17-2.23 (m, 1 H), 2.31-2.54 (m, 2 H), 4.11 (bs, 1 H), 5.38-5.40 (m, 1 H), 7.11 (s, 1 H), 7.16-7.36 (m, 15 H), 9.45 (s, 1 H).

Preparation of Intermediate Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenoate.

Sodium bis(trimethylsilyl)amide (22.9 mL of a 1.0 M solution in THF, 22.9 mmol, 1.0 equiv) was added to a solution of triethyl phosphonoacetate (5.59 g, 22.9 mmol, 1.0 equiv) in THF (200 mL) at -78 °C, and the resulting solution was stirred for 20 min at that temperature. Crude [BOC-L-(Tr-Glutaminal)]-H (10.8 g, 22.9 mmol, 1 equiv) in THF (50 mL) was added via cannula, and the reaction mixture was stirred for 2 h at -78 °C, warmed to 0 °C for 10 min, and partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 x 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) provided ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (10.9 g, 88%) as a white foam:

IR (thin film) 3321, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.2), 1.42 (s, 9 H), 1.70-1.78 (m, 1 H), 1.80-1.96 (m, 1 H), 2.35 (t, 2 H, J = 7.0), 4.18 (q, 2 H, J = 7.2), 4.29 (bs, 1 H), 4.82-4.84 (m, 1 H), 5.88 (dd, 1 H, J = 15.7, 1.6), 6.79 (dd, 1 H, J = 15.7, 5.3), 6.92 (s, 1 H), 7.19-7.34 (m, 15 H); Anal. ($C_{33}H_{38}N_2O_5$) C, H, N.

Preparation of Intermediate Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenoate (0.751 g, 1.38 mmol) was dissolved in 1,4-dioxane (5 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 5 mL) was added dropwise. The reaction solution was stirred for 2 h and then the solvent was evaporated to provide the amine salt as a foam which was used without purification. The crude amine salt was dissolved in dry CH_2Cl_2 (12 mL) under argon. 4-Methylmorpholine (1.05 mL, 9.55 mmol), hydroxybenzotriazole hydrate (0.280 g, 2.07 mmol), BOC-L-N-Me-Phe (0.386 g, 1.38 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.397 g, 2.07 mmol) were added successively. The reaction mixture was stirred overnight and poured into water (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (25% acetone in hexanes, then 3% MeOH in CH_2Cl_2) to provide ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate (0.450 g, 46%) as a foam: IR (thin film) 3318, 1708, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) (major rotamer) δ 1.28 (t, 3H, J = 7.2 Hz), 1.37 (s, 9H), 1.63-1.87 (m, 1H), 1.94-2.06 (m, 1H), 2.26-2.37 (m, 2H), 2.66 (s, 3H), 3.00 (dd, 1H, J = 13.5, 9.2 Hz), 3.29 (dd, 1H, J = 13.5, 6.4 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.51-4.70 (m, 2H), 5.71 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 8.1 Hz), 6.73 (dd, 1H, J = 15.6, 4.8 Hz), 6.97 (s, 1H), 7.12-7.36 (m, 20H); Anal. ($C_{43}H_{49}N_3O_6$) C, H, N.

Preparation of Intermediate Ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.433 g, 0.615 mmol) was dissolved in 1,4-dioxane (2.5 mL) and treated dropwise with a solution of hydrogen chloride in 1,4-dioxane (4.0 *M*, 2.5 mL). After stirring for 2 hours, the solvent was evaporated to provide ethyl-3-[L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate hydrochloride which was used without purification. One half of the crude amine salt formed was dissolved in dry CH_2Cl_2 (3 mL). 4-Methylmorpholine (0.169 mL, 1.54 mmol) and benzyl chloroformate (0.088 mL, 0.62 mmol) were added sequentially. After stirring overnight, the solvent was evaporated. The residue was purified by chromatography (20% to 25% acetone in hexanes) to provide ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.112 g, 49%) as a foam: IR (thin film) 3316, 1708, 1684, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer) δ 1.29 (t, 3H, J = 7.2 Hz), 1.59-1.72 (m, 1H), 1.82-2.01 (m, 1H), 2.19-2.26 (m, 2H), 2.73 (s, 3H), 2.99 (dd, 1H, J = 14.2, 9.2 Hz), 3.29 (dd, 1H, J = 14.2, 6.8 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.48-4.60 (m, 1H), 4.66 (dd, 1H, J = 9.2, 6.8 Hz), 4.93 (d, 1H, J = 12.3 Hz), 5.02 (d, 1H, J = 12.3 Hz), 5.71 (dd, 1H, J = 15.6, 1.6 Hz), 6.48 (d, 1H, J = 8.1 Hz), 6.70 (dd, 1H, J = 15.6, 5.4 Hz), 6.87 (s, 1H), 7.05-7.37 (m, 25H); Anal. ($C_{46}H_{47}N_3O_6$•0.5 H_2O) C, H, N.

Preparation of Product - Ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.096 g, 0.13 mmol) was dissolved in dry CH_2Cl_2 (4 mL). Triisopropylsilane (0.077 mL, 0.376 mmol) and trifluoroacetic acid (2 mL) were added sequentially to give a bright yellow solution. After stirring for 30 min, no yellow color remained. The solvents were evaporated to give a semi-solid residue which was purified by chromatography (5% methanol in CH_2Cl_2) to provide ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)- E-propenoate (0.061 g, 95%) as a colorless glass: IR (thin film) 3412, 3336, 3213, 1696, 1684, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) (major isomer) δ 1.28 (t, 3H, J = 7.2 Hz), 1.63-2.03 (m, 2H), 2.11-2.18 (m, 2H), 2.88 (s, 3H), 3.05 (dd, 1H, J= 14.0, 9.3 Hz), 3.31 (dd, 1H, J = 14.0, 6.8 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.51-4.63 (m, 1H), 4.71-4.80 (m, 1H), 4.95-5.16 (m, 2H), 5.73 (d, 1H, J = 15.9 Hz), 5.77-5.92 (m, 1H), 6.10 (s, 1H), 6.65-6.78 (m, 2H), 7.09-7.38 (m, 10H); Anal. ($C_{27}H_{33}N_3O_6$•0.75 H_2O) C, H, N.

Example 2 - Preparation of Compound 2: Ethyl-3-(CBZ-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.216 g, 0.308 mmol) was deprotected and coupled with CBZ-L-Leu (0.082 g, 0.309 mmol) using the procedure described for the formation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after two chromatographies (30% acetone/hexanes, then 2% methanol/CH_2Cl_2) as a glass (0.095 g, 36%): IR (thin film) 3304, 1708, 1659 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.63 (d, 3H, J = 6.7 Hz), 0.66 (d, 3H, J = 6.8 Hz), 0.83-0.89 (m, 6H), 1.12-1.48 (m, 4H), 1.26 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.51-1.66 (m, 2H), 1.69-1.80 (m, 1H), 1.88-2.04 (m, 2H), 2.16-2.32 (m, 4H), 2.90 (s, 6H), 2.95-3.17 (m, 2H), 3.25 (dd, 1H, J = 14.6, 3.4 Hz), 3.37 (dd, 1H, J = 13.7, 6.5 Hz), 4.11-4.25 (m, 2H), 4.17 (q, 4H, J = 7.2 Hz), 4.38-4.51 (m, 2H), 4.53-4.67 (m, 3H), 4.85-5.16 (m, 7H), 5.72 (d, 1H, J = 15.9 Hz), 5.95 (dd, 1H, J = 15.9, 1.2 Hz), 6.43 (d, 1H, J = 8.4 Hz), 6.74 (dd, 1H, J = 15.9, 5.3 Hz), 6.80 (s, 1H), 6.84 (dd, 1H, J = 15.9, 6.5 Hz), 7.09-7.38 (m, 50H), 8.00 (d, 1H, J = 7.8 Hz); Anal. ($C_{52}H_{58}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Product - Ethyl-3-(CBZ-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.056 g, 0.066 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-Phe-L-*Gln*]-E-propenoate (after chromatography, 5% MeOH in CH_2Cl_2) as a glass (0.029 g, 73%): IR (thin film) 3401, 3298, 3225, 1678, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.62-0.69 (m, 6H), 0.87-0.94 (m, 6H), 1.15-1.32 (m, 8H), 1.37-1.49 (m, 2H), 1.61-1.86 (m, 4H), 1.90-2.03 (m, 2H), 2.10-2.20 (m, 4H), 2.93 (s, 3H), 2.95 (s, 3H), 2.97-3.11 (m, 1H), 3.17-3.28 (m, 2H), 3.41-3.49 (m, 1H), 4.16-4.29 (m, 5H), 4.42-4.52 (m, 2H), 4.55-4.71 (m, 3H), 4.95-5.12 (m, 4H), 5.39-5.52 (m, 4H), 5.78 (d, 1H, J = 15.9 Hz), 5.89 (s, 1H), 6.00 (dd, 1H, J = 15.9, 1.2 Hz), 6.08 (s, 1H), 6.73-6.91 (m, 3H), 7.12-7.37 (m, 20H), 7.98 (d, 1H, J = 8.1 Hz); Anal. ($C_{33}H_{44}N_4O_7$•0.5 H_2O) C, H, N.

Example 3 - Preparation of Compound 3: Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.545 g, 1.00 mmol) was deprotected and coupled with the dicyclohexylamine salt of BOC-L-N-Me-(OMe)-Tyr (0.630 g, 1.28 mmol) using the procedure described in Example 1 for the formation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (after chromatography, 33% EtOAc in hexanes) as a white foam (0.380 g, 52%): IR (thin film) 3307, 1708, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 1.38 (s, 9H), 1.60-1.77 (m, 1H), 1.94-2.07 (m, 1H), 2.27-2.36 (m, 2H), 2.67 (s, 3H), 2.89-2.99 (m, 1H), 3.18-3.27 (m, 1H), 3.78 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 4.44-4.65 (m, 2H), 5.73 (d, 1H, J = 15.6 Hz), 6.35 (d, 1H, J = 8.7 Hz), 6.69-6.84 (m, 3H), 6.94 (s, 1H), 7.04-7.12 (m, 2H), 7.17-7.34 (m, 15H); Anal. ($C_{44}H_{51}N_3O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (0.360 g, 0.491 mmol) was dissolved in 1,4-dioxane (2 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 2 mL) was added dropwise. The reaction solution was stirred for 2 h, and then the solvent was evaporated to provide the amine salt as a foam which was used without purification. The crude amine salt was dissolved in dry CH_2Cl_2 (12 mL) under argon. 4-Methylmorpholine (0.208 mL, 1.89 mmol), CBZ-L-Leu (0.125 g, 0.471 mmol), hydroxybenzotriazole hydrate (0.096 g, 0.71 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.136 g, 0.709 mmol) were added successively. After stirring overnight, 4-methylmorpholine (0.208 mL, 1.89 mmol), hydroxybenzotriazole hydrate (0.096 g, 0.71 mmol), CBZ-L-Leu (0.125 g, 0.471 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.136 g, 0.709 mmol) were added again. Then 4-dimethylaminopyridine (0.010 g, 0.082 mmol) was added. After

stirring 48 h more, the reaction mixture was poured into water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3x 75 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (38% to 50% EtOAc in hexanes) to provide ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (0.210 g, 51%) as a colorless glass: IR (thin film) 3295, 1708, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.65 (d, J = 6.5 Hz), 0.68 (d, J = 6.8 Hz), 0.82-0.91 (m), 1.14-1.50 (m), 1.52-1.66 (m), 1.68-1.81 (m), 1.87-2.02 (m), 2.16-2.28 (m), 2.89 (s), 2.92 (s), 2.95-3.09 (m), 3.14-3.23 (m), 3.24-3.33 (m), 3.76 (s), 3.76 (s), 4.08-4.25 (m), 4.41-4.49 (m), 4.54-4.63 (m), 4.83-5.16 (m), 5.73 (d, J = 15.6 Hz), 5.95 (dd, J = 15.7, 1.1 Hz), 6.40 (d, J = 8.4 Hz), 6.74 (dd, J = 15.6, 5.0 Hz), 6.78-6.87 (m), 6.99-7.06 (m), 7.16-7.34 (m), 7.97 (d, J = 7.8 Hz); Anal. ($C_{53}H_{60}N_4O_8 \bullet 0.5\ H_2O$) C, H, N.

Preparation of Product -
Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-(Tr-*Gln*)]-E-propenoate (0.128 g, 0.145 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-[CBZ-L-Leu-L-N-Me-(OMe)-Tyr-L-*Gln*]-E-propenoate (after chromatography, 5% MeOH in CH_2Cl_2) as a colorless glass (0.083 g, 89%): IR (thin film) 3401, 3295, 3201, 1708, 1666, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of rotamers) δ 0.64-0.71 (m), 0.87-0.94 (m), 1.27 (t, J = 7.2 Hz), 1.28 (t, J = 7.2 Hz), 1.38-1.51 (m), 1.61-1.85 (m), 1.87-2.02 (m), 2.07-2.21 (m), 2.80-2.92 (m), 2.94 (s), 2.96 (s), 2.97-3.06 (m), 3.08-3.21 (m), 3.36 (dd, J = 14.0, 6.2 Hz), 3.76 (s), 4.16-4.28 (m), 4.18 (q, J = 7.2 Hz), 4.45-4.66 (m), 4.94-5.12 (m), 5.52 (d, J = 7.8 Hz), 5.58 (d, J = 7.8 Hz), 5.69 (s), 5.77 (d, J = 15.9 Hz), 5.99 (s), 6.00 (dd, J = 15.9, 1.2 Hz), 6.21 (s), 6.76 (dd, J = 15.9, 5.3 Hz), 6.79-6.91 (m), 7.02-7.10 (m), 7.26-7.37 (m), 7.97 (d, J = 8.1 Hz); ($C_{34}H_{46}N_4O_8 \bullet 0.5\ H_2O$) C, H, N.

Example 4 - Preparation of Compound 5: Ethyl-3-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Cyclopentyl Chlorothiolformate.

Cyclopentanethiol (10.7 mL, 0.1 mol) was dissolved in 200 mL of CH_2Cl_2. Triphosgene (11.13 g, 37.5 mmol) was added, and the reaction mixture was cooled to 0 °C. Et_3N (14.1 mL, 0.1 mol) was added dropwise, and the reaction was allowed to warm to room temperature over a period of one hour. The solvent was carefully removed under reduced pressure at 20 °C due to the volatility of the product. The resulting residue was taken up in Et_2O, and the solids were filtered and washed with more Et_2O. The solvent was again carefully removed under reduced pressure, and the product was purified by distillation (85% yield): colorless liquid (bp 70-74 °C; 1 torr): IR(neat) 1756, 830 cm^{-1}; ^1H NMR (benzene-d_6) δ 1.01-1.23 (m, 6H), 1.49-1.60 (m, 2H), 3.20-3.29 (m, 1H).

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-OBn.

The p-toluenesulfonic acid salt of L-Leu-OBn (3.14 g, 8.0 mmol) was dissolved in 70 mL of CH_2Cl_2, followed by 2.25 mL (16 mmol) of Et_3N. Cyclopentyl chlorothiolformate (1.32 g, 8.0 mmol) was dissolved in 10 mL of CH_2Cl_2 and added dropwise to the reaction. The reaction was stirred one hour, and the solvent was removed in vacuo. The product was purified by flash silica gel chromatography eluting with 5% EtOAc/ hexanes to give 2.48 g (71%) of a clear oil; IR(KBr) 3318, 2959, 2870, 1744, 1649, 1516, 1186, 854, 746, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.82 (d, 3H, J = 6.0 Hz), 0.86 (d, 3H, J = 6.0 Hz), 1.39-1.70 (m, 9H), 1.97 (m, 2H), 3.55 (quint, 1H, J = 7.0 Hz), 4.23 (m, 1H), 5.09 (d, 1H, J = 12.5 Hz), 5.13 (d, 1H, J = 12.5 Hz), 7.35 (m, 5H), 8.48 (d, 1H, J = 7.7 Hz). Anal. ($C_{19}H_{27}NO_3S$) C, H, N.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu.

Cyclopentylthiocarbonyl-L-Leu-OBn (2.42 g, 6.92 mmol) was dissolved in 35 mL of CH_2Cl_2, followed by 4.51 mL (41.5 mmol) of anisole. The reaction was cooled to 0 °C, and $AlCl_3$ (2.88 g, 21.6 mmol), dissolved in 35 mL of nitromethane, was added dropwise via pipet. The ice bath was removed, and the reaction was allowed to stir at rt for 5 h. The

reaction was diluted with EtOAc and washed with 10% HCl. The organic phase was washed with a sat. $NaHCO_3$ solution. The basic solution was then reacidified to a pH = 1 with 10% HCl, and the product was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 0.23 g (93%) of an opaque oil: IR(neat) 3302-2473 (bs), 1715, 1652, 1532, 1202, 925, 852, 673, 563 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.82 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.40-1.70 (m, 9H), 1.98 (m, 2H), 3.53 (quint, 1H, J = 7.0 Hz), 4.18 (m, 1H), 8.29 (d, 1H, J = 8.0 Hz), 12.58 (bs). Anal. ($C_{12}H_{21}NO_3S$) C, H, N.

Preparation of Intermediate CBZ-L-(Tr-Gln).

CBZ-L-Gln (28.03 g, 100 mmol) was dissolved in 300 mL of glacial acetic acid. To this solution was added triphenylmethanol (26.83 g, 100 mmol), acetic anhydride (18.87 mL, 200 mmol), and 0.5 mL of conc. sulfuric acid. The reaction was heated to 55 °C and stirred for one hour. After cooling to room temperature, the mixture was concentrated under reduced pressure to one-third the original volume. Ice water was added, and the product extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was recrystallized from CH_2Cl_2/hexane, and the resulting crystals washed with Et_2O, yielding 37.27 g (71%) as a white solid: IR (KBr) 3418, 3295, 3059, 3032, 2949, 2515, 1699, 1628, 1539, 1504, 1447, 1418, 1341, 1242, 1209, 1061, 748, 696 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.71 (m, 1 H), 1.88 (m, 1 H), 2.38 (m, 2 H), 3.97 (m, 1 H), 5.04 (s, 2 H), 7.14-7.35 (m, 20H), 7.52 (d, 1 H, J = 7.7 Hz), 8.60 (s, 1 H).

Preparation of Intermediate CBZ-L-(Tr-Gln)OMe.

CBZ-L-(Tr-Gln) (0.26 g, 0.5 mmol) was added to a stirring solution of 0.25 mL of acetyl chloride in 5 mL of MeOH, and stirring was continued at room temperature for 1 h. The solvent was removed in vacuo, and the residue dissolved in 100 mL CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$, and brine, followed by drying over Na_2SO_4. The crude product was purified on a short flash silica gel column, eluting with 20% EtOAc/hexane. The product (0.23 g, 84%) was obtained as a white solid: IR (KBr) 3405, 3277, 3057, 3034, 2953, 1724, 1643, 1532, 1493, 1447, 1207, 1042, 750, 698 cm^{-1};

^{1}H NMR (DMSO-d_6) δ 1.16 (t, 1 H, J = 7.0 Hz), 1.77 (m, 1 H), 1.97 (m, 1H), 3.61 (s, 3H), 4.99 (m, 1H), 5.03 (s, 2H), 7.02-7.55 (m, 20H), 7.69 (d, 1H, J = 7.7 Hz), 8.59 (s, 1H). Anal. ($C_{33}H_{32}N_2O_5$) C, H, N.

Preparation of Intermediate CBZ-L-(Tr-Glutaminol).

CBZ-L-(Tr-Gln)OMe (1.50 g, 2.79 mmol) was dissolved in 20 mL of THF and 10 mL of EtOH. LiCl (0.24 g, 5.6 mmol) was added, and the mixture stirred for 10 minutes until all solids had dissolved. $NaBH_4$ (0.21 g, 5.6 mmol) was added, and the reaction was stirred overnight at room temperature. The solvents were removed in vacuo, the residue taken up in water, and the pH was adjusted to 2-3 with 10% HCl. The product was extracted with EtOAc, and the organic layer was washed with water and brine before drying over $MgSO_4$. The crude product was purified on a short flash silica gel column, eluting with an increasing gradient of EtOAc/benzene, yielding 1.02 g (72%) of a white glassy solid: IR (KBr) 3408, 3318, 3057, 3032, 2947, 1699, 1674, 1516, 1447, 1240, 1059, 752, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 1H), 1.72 (m, 1H), 2.26 (m, 2H), 3.17-3.50 (m, 3H), 4.64 (t, 1H, J = 5.0 Hz), 5.00 (s, 2H), 7.00-7.40 (m, 20H), 6.96 (d, 1H, J = 8.5 Hz), 8.54 (s, 1H). Anal. ($C_{32}H_{32}N_2O_4$) C, H, N.

Preparation of Intermediate L-(Tr-Glutaminol).

10% Pd on carbon (0.03 g) was added to a solution of CBZ-L-(Tr-Glutaminol) (0.51 g, 1.0 mmol) in 20 mL MeOH, with stirring, and under an argon atmosphere. The reaction vessel was evacuated under vacuum and then put under an atmosphere of hydrogen using a balloon. The mixture was stirred for 4 h. At this time the hydrogen gas was evacuated and the catalyst was removed by filtration. The solvent was removed under vacuum to give a white solid in 98% yield which was used without further purification: IR (KBr) 3255, 3057, 3016, 2916, 1642, 1527, 1491, 1446, 1057, 1036, 750, 700, 636 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.29 (m, 1H), 1.53 (m, 1H), 2.29 (m, 2H), 3.08 (m, 1H), 3.18 (m, 2H), 3.38 (bs, 2H), 4.43 (bs, 1H), 7.14-7.28 (m, 15H), 8.62 (s, 1H). Anal. ($C_{24}H_{26}N_2O_2$) C, H, N.

Preparation of Intermediate CBZ-L-N-Me-Phe-L-(Tr-Glutaminol).

CBZ-N-Me-L-Phe (2.24 g, 7.14 mmol) was dissolved in 70 mL of THF. Carbonyldiimidazole (1.16 g, 7.14 mmol) was added, and the reaction was stirred for one hour at rt. L-(Tr-Glutaminol) (2.80 g, 7.5 mmol) was added, and the reaction was stirred overnight. At this time the solvent was removed in vacuo, and the product was purified by column chromatography on silica gel using a gradient solvent system (0-2% $MeOH/CHCl_3$) to give 3.37 g (70%) of a white amorphous solid: IR(KBr) 3304, 3057, 3028, 2949, 1668, 1495, 1447, 1142, 750, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.51 (m, 1H), 1.73 (m, 1H), 2.23 (m, 2H), 2.79 (s, 3H), 2.84 (m, 1H), 3.29 (m, 3H), 3.70 (m, 1H), 4.66 (m, 1H), 4.88 (m, 3H), 7.15-7.28 (m, 25H), 7.69 (m, 1H), 8.55 (m, 1H). MS calcd for $C_{42}H_{43}N_3O_5$+H 670, found 670.

Preparation of Intermediate L-N-Me-Phe-L-(Tr-Glutaminol).

CBZ-L-N-Me-Phe-L-(Tr-glutaminol) (3.33 g, 4.97 mmol) was dissolved in 35 mL of MeOH. The reaction was placed under slight vacuum, and then under an argon atmosphere. With care, 10% Pd/C (0.33 g) was added. The flask was purged of argon which was replaced by hydrogen gas using a balloon. The reaction mixture was stirred at room temperature for 4.5 h, at which time the flask was purged of hydrogen and the catalyst was filtered off. Solvent was removed in vacuo to give 2.36 g (89%) of a white amorphous solid: IR(KBr) 3302, 3057, 3024, 2937, 1655, 1522, 1493, 1447, 750, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (m, 1H), 1.67 (m, 1H), 2.13 (m, 1H), 2.16 (s, 3H), 2.24 (m, 1H), 2.68 (dd, 1H, J = 13.5, 7.3 Hz), 2.82 (dd, 1H, J = 13.5, 5.8 Hz), 3.10 (m, 2H), 3.25 (m, 1H), 3.67 (m, 1H), 4.63 (t, 1H, J = 5.5 Hz), 7.13-7.28 (m, 21H), 7.54 (d, 1H, J = 8.8 Hz), 8.54 (s, 1H). Anal. ($C_{34}H_{37}N_3O_3$) C, H, N.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminol).

This preparation was carried out following the procedure of L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397, the disclosure of which is entirely incorporated herein by reference. Cyclopentylthiocarbonyl-L-Leu (0.27 g, 1.05 mmol) was dissolved in 3.5 mL of

DMF. Diisopropylethylamine (0.37 mL, 2.10 mmol) was added, followed by 0.56 g (1.05 mmol) of L-N-Me-Phe-L-(Tr-glutaminol). The reaction was cooled to 0 °C and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.398 g, 1.05 mmol) was added. The reaction mixture was allowed to warm to room temperature whereupon the DMF was removed in vacuo. The residue was dissolved with EtOAc, and the organic phase washed consecutively with 10% HCl solution, saturated $NaHCO_3$ solution, H_2O, and brine. The solvent was dried ($MgSO_4$), filtered, and concentrated to give a residue which was subjected to flash column chromatography on silica gel (gradient; 0-1% MeOH/$CHCl_3$) to give 0.49 g (60%) of a white amorphous solid: IR(KBr) 3293, 3057, 3024, 2955, 2868, 1634, 1493, 1447, 1205, 752, 700 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.18 (m), 0.62 (m), 0.79 (d, J = 6.3 Hz), 1.00-2.05 (m), 2.08-2.40 (m), 2.81 (s), 2.88 (m), 2.95 (s), 3.05-3.53 (m), 3.65 (m), 3.79 (m), 4.27 (m), 4.61 (m), 5.11 (m), 7.14-7.28 (m), 7.43 (d, J = 8.0 Hz), 7.64 (d, J = 8.8 Hz), 8.17 (d, J = 8.0 Hz), 8.43 (d, J = 7.0 Hz), 8.51 (s). MS calcd for $C_{46}H_{56}N_4O_5S$+Cs 909, found 909.

Preparation of Intermediate Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminal).

To cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) (0.57 g, 0.73 mmol) dissolved in 7 mL of DMSO was added o-iodoxybenzoic acid (0.61 g, 2.19 mmol). The reaction mixture was stirred at rt for 1.5 h. The DMSO was then removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and reconcentrated to remove any residual DMSO. Dilution with CH_2Cl_2 and reconcentration was repeated, and the residue was diluted with EtOAc to give a white precipitate which was filtered off. The solvent was washed with a 5% $Na_2S_2O_3$/5% $NaHCO_3$ solution, water, and brine before drying over $MgSO_4$. Removal of the solvent under vacuum gave 0.41 g (72%) of a white glassy solid which was used immediately without further purification: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.03 (m), 0.62 (m), 1.04-2.10 (m), 2.20-2.45 (m), 2.82 (s), 2.90 (m), 2.94 (s), 3.21 (m), 4.00 (m), 4.14 (m), 4.34 (m), 4.62 (m), 4.81 (m), 5.17 (m), 7.14-7.28 (m), 8.15 (d, J = 7.0 Hz), 8.25 (d, J = 7.0 Hz), 8.35 (d, J = 7.0 Hz), 8.41 (d, J = 7.0 Hz), 8.57 (s), 8.62 (s), 9.27 (s), 9.43 (s).

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Cyclopentylthiocarbonyl-L-Leu-N-Me-L-Phe-L-(Tr-glutaminal) (0.19 g, 0.25 mmol) was dissolved in 5 mL of THF. (Carbethoxymethylene)triphenylphosphorane (0.10 g, 0.30 mmol) was added, and the reaction was stirred overnight at rt. The solvent was removed in vacuo, and the residue purified by flash column chromatography on silica gel (gradient; 0-0.75 % MeOH/$CHCl_3$) to give 0.25 g of material that was contaminated by triphenylphosphine oxide. This material was used without further purification: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.16 (m), 0.62 (m), 0.79 (d, J = 6.3 Hz), 1.10 (m), 1.20 (t, J = 7.0 Hz), 1.30-1.78 (m), 1.95 (m), 2.10-2.42 (m), 2.80 (s), 2.88 (m), 2.95 (s), 3.16 (m), 3.48 (m), 4.10 (q, J = 7.0 Hz), 4.11 (q, J = 7.0 Hz), 4.37 (m), 4.53 (m), 4.63 (m), 4.81 (m), 5.06 (m), 5.66 (d, J = 16.0 Hz), 5.93 (d, J = 16.0 Hz), 6.71 (dd, J = 16.0, 6.0 Hz), 6.80 (d, J = 16.0, 6.0 Hz), 7.13-7.28 (m), 7.97 (d, J = 8.0 Hz), 8.07 (d, J = 8.0 Hz), 8.16 (d, J = 7.0 Hz), 8.49 (d, J = 6.0 Hz), 8.55 (s), 8.60 (s).

Preparation of Product Ethyl-3-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.25 g) was dissolved in 5 mL of CH_2Cl_2. Trifluoroacetic acid (0.5 mL) was added, and the reaction was stirred at rt for 4 h. The solvent was removed in vacuo, and the residue purified by flash column chromatography on silica gel (gradient; 0-2 % MeOH/$CHCl_3$) to give 0.11 g (74% for two steps from the aldehyde intermediate) as a white amorphous solid: mp = 68-72 °C; IR(KBr) 3283, 2955, 1634, 1531, 1277, 1205 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.26 (m), 0.61 (m), 0.82 (d, J = 6.3 Hz), 0.83 (d, J = 6.3 Hz), 1.13 (m), 1.20 (t, J = 7.0 Hz), 1.30-2.12 (m), 2.77 (s), 2.90 (m), 2.94 (s), 3.11 (m), 3.47 (m), 4.10 (q, J = 7.0 Hz), 4.11 (q, J = 7.0 Hz), 4.38 (m), 4.50 (m), 4.67 (m), 4.81 (m), 5.04 (m), 5.69 (d, J = 15.0 Hz), 5.99 (d, J = 15.0 Hz), 6.72 (dd, J = 15.0, 5.5 Hz), 6.76 (bs), 6.83 (d, J = 15.0, 5.5 Hz), 7.12-7.30 (m), 7.99 (d, J = 8.0 Hz), 8.04 (d, J = 8.0 Hz), 8.19 (d, J = 8.0 Hz), 8.52 (d, J = 6.0 Hz). HRMS calcd for $C_{31}H_{46}N_4O_6S$+Cs 735.2192, found 735.2174. Anal. ($C_{31}H_{46}N_4O_6S$) C, H, N.

Example 5 - Preparation of Compound 6: 2-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, this intermediate was synthesized from cyclopentylthiocarbonyl-L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminal) (0.205 g, 0.264 mmol) and α-(triphenylphosphoranylidene)-γ-butyrolactone (0.12 g, 0.343 mmol) (prepared from α-bromo-γ-butyrolactone according to the procedure of J. E. Baldwin, et al., *Tetrahedron*; **1992**, *48*, 9373, the disclosure of which is entirely incorporated herein by reference) in 5 mL THF to give 0.28 g of product contaminated with triphenylphosphine oxide which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.12 (m), 0.60 (m), 0.79 (d, J= 6.3 Hz), 1.10-2.18 (m), 2.10-2.49 (m), 2.80 (s), 2.89 (m), 2.94 (s), 3.09-3.57 (m), 4.30 (m), 4.42 (m), 4.85 (m), 5.01 (m), 6.26 (m), 6.42 (m), 7.10-7.29 (m), 8.01 (d, J= 8.0 Hz), 8.06 (d, J= 8.0 Hz), 8.18 (d, J= 7.0 Hz), 8.48 (d, J= 7.0 Hz), 8.53 (s), 8.59 (s).

Preparation of Product - 2-(Cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γButyrolactone).

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, 2-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) was synthesized from 2-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) in 49% yield (two steps from the aldehyde): white amorphous solid: mp = 87-91 °C: IR(KBr) 3286, 2963, 1749, 1668, 1634, 1531, 1452, 1205, 1138 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.12 (m), 0.58 (m), 0.83 (m), 1.08 (m), 1.20-1.79 (m), 2.01 (m), 2.77 (s), 2.84 (m), 2.94 (s), 3.12 (m), 3.53 (m), 4.26-4.43 (m), 4.68 (m), 4.96 (m), 6.26 (m), 6.39 (m), 6.76 (bs), 7.12-7.27 (m), 8.04 (m), 8.19 (d, J= 8.0 Hz), 8.50 (d, J= 7.0 Hz). HRMS calcd for $C_{31}H_{44}N_4O_6S$+Cs 733.2036, found 733.2053. Anal. ($C_{31}H_{44}N_4O_6S$ •0.75 $CHCl_3$) C, H, N.

Example 6 - Preparation of Compound 7: 1-(2',3'-Dihydroindolin-1-yl)-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.

Preparation of Intermediate BOC-L-Leu-L-N-Me-Phe-OMe.

N-Me-Phe-OMe•HCl (1.4 g) was dissolved in CH_2Cl_2 (50 mL) and poured into a combination of 1 N NaOH (aq, 7 mL) and sat. $NaHCO_3$ (25 mL). After mixing, the organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give the free amine as a clear colorless oil (1.14 g, 5.90 mmol). A solution of this amine and diisopropylethylamine (1.13 mL, 6.49 mmol) in DMF (10 mL) was added dropwise to a 0 °C solution of BOC-L-Leu (1.50 g, 6.49 mmol) and hydroxybenzotriazole hydrate (0.877 g, 6.49 mmol) in DMF (10 mL). Dicyclohexylcarbodiimide (1.47 g, 7.12 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, and was then stirred at rt for 48 h. The mixture was filtered to remove the precipitate, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with sat. $NaHCO_3$ (40 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography (25% EtOAc in hexanes) to give BOC-L-Leu-L-N-Me-Phe-OMe as a white solid (2.04 g, 85%): mp = 126-127 °C; IR (thin film) 3401, 3319, 1743, 1708, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer) δ 0.92 (d, 3H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.5 Hz), 1.32-1.48 (m, 2H), 1.41 (s, 9H), 1.61-1.77 (m, 1H), 2.90 (s, 3H), 3.04 (dd, 1H, J = 14.5, 10.5 Hz), 3.37 (dd, 1H, J = 14.5, 5.5 Hz), 3.72 (s, 3H), 4.48-4.57 (m, 1H), 4.98-5.04 (m, 1H), 5.20 (dd, 1H, J = 10.5, 5.5 Hz), 7.16-7.32 (m 5H); Anal. ($C_{22}H_{34}N_2O_5$) C, H, N.

Preparation of Intermediate BOC-L-Leu-L-N-Me-Phe.

BOC-L-Leu-L-N-Me-Phe-OMe (0.625 g, 1.54 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C. A solution of 2 N NaOH (aq, 6.15 mL, 12.3 mmol) was added dropwise. The reaction mixture was stirred for 3 h at rt and poured into 10% aq $KHSO_4$ (150 mL). This mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated to give BOC-L-Leu-L-N-Me-Phe as a white foam (0.617 g, quantitative yield) which was used without purification.

Preparation of Intermediate [2-(2,3-Dihydroindol-1-yl)-2-oxo-ethyl]-Phosphonic Acid Diethyl Ester.

Oxalyl chloride (5.96 mL, 68.3 mmol) was added to a solution of diethylphosphonoacetic acid (12.8 g, 65.0 mmol) and DMF (0.03 mL, 0.39 mmol) in benzene (150 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 1 °h and then was concentrated under reduced pressure. The resulting oil was dissolved in THF (30 mL) and was added via cannula to a solution of indoline (7.38 g, 61.9 mmol) and triethylamine (10.9 mL, 78.0 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then it was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a tan solid. Recrystallization from Et_2O provided [2-(2,3-dihydroindol-1-yl)-2-oxo-ethyl]- phosphonic acid diethyl ester (12.2 g, 63%) as a light brown solid: mp = 97-99 °C; IR (KBr) 3460, 1657, 1597, 1482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 6H, J = 7.2), 3.14 (d, 2H, J = 22.4), 3.22 (d, 2H, J = 8.4), 4.15-4.30 (m, 6H), 7.04 (t, 1H, J = 7.0), 7.17-7.28 (m, 2H), 8.21 (d, 1H, J = 9.0); Anal. ($C_{14}H_{20}NO_4P$) C, H, N.

Preparation of Intermediate 1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-Propenone.

Sodium bis(trimethylsilyl)amide (11.9 mL of a 1.0 M solution in THF, 11.9 mmol, 1.0 equiv) was added to a solution of [2-(2,3-dihydroindol-1-yl)-2-oxo-ethyl]-phosphonic acid diethyl ester (3.54 g, 11.9 mmol, 1.0 equiv) in THF (150 mL) at -78 °C, and the resulting solution was stirred for 20 min at that temperature. Crude BOC-L-(Tr-Glutaminal) (5.63 g, 11.9 mmol, 1 equiv) in THF (40 mL) was added via cannula, and the reaction mixture was stirred for 1 h at -78 °C, warmed to 0 °C for 10 min, and partitioned between 0.5 M HCl (150 mL) and EtOAc (2 x 150 mL). The organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (50% EtOAc in hexanes) provided 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone as an off-white foam: IR (thin film) 3401, 3307, 1690, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.76-2.05 (m, 2H), 2.37-4.06 (m, 2H), 3.11-3.22 (m, 2H), 4.02-4.16 (m, 2H),

4.27-4.40 (m, 1H), 4.91-4.97 (m, 1H), 6.29 (d, 1H, $J = 14.9$), 6.77-6.96 (m, 2H), 6.98-7.05 (m, 1H), 7.14-7.37 (m, 17H), 8.25 (d, 1H, $J = 7.5$); Anal. ($C_{39}H_{41}N_3O_4$) C, H, N.

Preparation of Intermediate 1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.420 g, 0.682 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 3 mL) was added dropwise. After stirring for 2 h, the solvent was evaporated to give the amine salt which was used without purification. This crude amine salt was coupled to BOC-L-Leu-L-N-Me-Phe (0.302 g, 0.769 mmol) using the procedure described in Example 6 for the formation of BOC-L-Leu-L-N-Me-Phe-OMe to give 1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (after chromatography, 43% EtOAc in hexanes to 100% EtOAc) as an off-white foam (0.323 g, 53%): IR (thin film) 3401, 3295, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, $J = 6.5$ Hz), 0.85 (d, $J = 6.8$ Hz), 0.88 (d, $J = 6.5$ Hz), 1.04-1.21 (m), 1.23-1.48 (m), 1.34 (s), 1.41 (s), 1.56-1.67 (m), 1.82-1.94 (m), 1.95-2.09 (m), 2.26-2.36 (m), 2.90 (s), 2.99 (dd, $J = 14.3$, 10.4 Hz), 3.13-3.22 (m), 3.30 (dd, $J = 14.3$, 3.6 Hz), 3.97-4.18 (m), 4.38-4.47 (m), 4.55-4.77 (m), 4.83-4.90 (m), 6.18 (d, $J = 14.0$ Hz), 6.35-6.46 (m), 6.72 (s), 6.82-6.91 (m), 6.99-7.35 (m), 8.17 (d, $J = 8.4$ Hz), 8.25 (d, $J = 8.1$ Hz); Anal. ($C_{55}H_{63}N_5O_6 \cdot 0.75\ H_2O$) C, H, N.

Preparation of Intermediate 1-(2',3'-Dihydroindolin-1-yl)-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (0.315 g, 0.355 mmol) was dissolved in 1,4-dioxane (6 mL). A solution of HCl in 1,4-dioxane (4.0 *M*, 4 mL) was added dropwise. After stirring for 2 h, the solvent was evaporated to give the amine salt which was used without purification. This crude amine salt was dissolved in dry CH_2Cl_2 (8 mL) under argon, and diisopropylethylamine (0.136 mL, 0.781 mmol) was added. Ethyl chlorothiolformate (0.044 mL, 0.422 mmol) was added. The reaction solution was stirred 2 h and then poured into water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases

were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (50%-67% EtOAc in hexanes) to give 1-(2',3'-Dihydroindolin-1-yl)-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenone as a white foam (0.127 g, 41%): IR (thin film) 3284, 1660, 1637, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.59-0.76 (m), 0.82-0.89 (m), 1.15 (t, J = 7.3 Hz), 1.24 (t, J = 7.3 Hz). 1.32-1.44 (m), 1.52-1.76 (m), 1.83-2.11 (m), 2.04 (s), 2.25-2.36 (m), 2.63-3.41 (m), 2.88 (s), 2.89 (s), 3.94-4.19 (m), 4.34-4.44 (m), 4.50-4.72 (m), 5.82 (d, J = 7.5 Hz), 5.92 (d, J = 7.5 Hz), 6.22 (d, J = 14.6 Hz), 6.38 (d, J = 15.0 Hz), 6.65 (d, J = 8.4 Hz), 6.72-6.95 (m), 6.99-7.06 (m), 7.08-7.34 (m), 8.03 (d, J = 7.8 Hz), 8.22-8.28 (m); Anal. ($C_{53}H_{59}N_5O_5S$) C, H, N.

Preparation of Product 1-(2',3'-Dihydroindolin-1-yl)-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.

1-(2',3'-Dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone (0.110 g, 0.125 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give 1-(2',3'-dihydroindolin-1-yl)-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenone (after chromatography, 8% MeOH in CH_2Cl_2, and evaporation from Et_2O) as a white waxy material (0.044 g, 55%): IR (thin film) 3389, 3284, 3213, 1660, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.61-0.78 (m), 0.91 (d, J = 6.5 Hz), 0.92 (d, J = 6.2 Hz), 1.18-1.34 (m), 1.39-1.57 (m), 1.58-1.85 (m), 1.87-2.11 (m), 2.15-2.33 (m), 2.72-3.31 (m), 2.96 (s), 3.41-3.50 (m), 4.03-4.20 (m), 4.42-4.77 (m), 5.78 (d, J = 12.4 Hz), 6.01 (s, bs), 6.26-6.49 (m), 6.57 (d, J = 7.2 Hz), 6.80-6.97 (m), 6.99-7.35 (m), 7.91 (d, J = 8.1 Hz), 8.22-8.30 (m); Anal. ($C_{34}H_{45}N_5O_5S$) C, H, N.

Example 7 - Preparation of Compound 8: 2-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[BOC-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

BOC-L-(Tr-glutaminal) (290 mg, 0.614 mmol) and α-(triphenylphosphoranylidene)-γ-butyrolactone (255 mg, 0.737 mmol) (prepared from α-bromo-γ-butyrolactone according to the procedure of J. E. Baldwin, et al., *Tetrahedron*; 1992, *48*, 9373, the disclosure of which is entirely incorporated herein by reference) were refluxed in DME (15 mL) / DMF

(2 mL) for 2 h. Solvents were removed under vacuum, and the residue was purified by flash chromatography eluting with 50% EtOAc / hexane on silica gel to give 235 mg of 2-[BOC-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) as a white solid in 71% yield: IR (KBr) 3399, 3059, 2976, 2926, 1752, 1688, 1493, 1366, 1248, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.84 (m, 2 H), 2.38 (q, 2 H, J = 6.4 Hz) 2.80 (m, 1 H), 2.97 (m, 1 H), 4.22 (m, 1 H), 4.33 (t, 2 H, J = 7.2 Hz), 4.81 (m, 1 H), 6.43 (m, 1 H), 6.80 (s, 1 H), 7.19-7.32 (m, 15 H). Anal. ($C_{33}H_{36}N_2O_5$•H_2O) C, H, N.

Preparation of Intermediate 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.577 g, 1.03 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 M, 3 mL) was added dropwise. The solution was stirred at rt for 2 h, at which time the solvent was evaporated to provide the amine HCl salt which was used without purification. The crude salt and BOC-L-Leu-L-N-Me-Phe (0.288 g, 1.03 mmol) were dissolved in dry CH_2Cl_2 (15 mL). Hydroxybenzotriazole-hydrate (0.209 g, 1.55 mmol), 4-methylmorpholine (0.34 mL, 3.09 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbarbodiimide hydrochloride (0.296 g, 1.55 mmol) were added successively. The reaction mixture was stirred at rt overnight and poured into water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.691 g, 82 %) as white foam: IR (thin film) 3301, 2958, 1753, 1675, 1494, 1173, 728 cm^{-1}; ^{1}H NMR (mixture of rotamers) ($CDCl_3$) δ 0.63-0.66 (m), 0.71-0.75 (m), 1.03-1.13 (m), 1.37 (s), 1.38 (s), 1.41 (s), 1.42 (s), 1.81-2.00 (m), 2.26-2.29 (m), 2.73-3.06 (m), 3.27 (d, J = 3.3 Hz), 3.32 (d, J = 3.3 Hz), 3.60-3.68 (m), 4.27-4.38 (m), 4.87 (d, J = 7.2 Hz), 6.50 (t, J = 3.3 Hz), 6.53 (t, J = 3.3 Hz), 6.70 (s), 7.09-7.13 (m), 7.19-7.34 (m), 7.44-7.50 (m), 7.64-7.71 (m), 8.21 (d, J = 3.6 Hz). Anal. ($C_{49}H_{58}N_4O_7$•0.45 H_2O) C, H, N.

Preparation of Intermediate 2-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.652 g, 0.8 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of HCl in 1,4-dioxane (4.0 M, 3 mL) was added dropwise. The solution was stirred at rt for 2 h, and the solvent was evaporated to provide the amine HCl salt which was used without purification. The crude amine HCl salt was dissolved in dry CH_2Cl_2 (10 mL), and Et_3N (0.335 mL, 2.4 mmol) was added. The reaction mixture was cooled to 0 °C, and ethyl chlorothiolformate (0.083 mL, 0.8 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h and then poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) as a white foam (0.389 g, 60%): IR (thin film) 3294, 2361, 1752, 1636, 1522, 1206 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$): δ 0.62-0.68 (m), 0.87 (d, 6.6 Hz), 1.19-1.29 (m), 1.37-1.42 (m), 1.89-1.94 (m), 2.28-2.31 (m), 2.71-3.12 (m), 3.65-3.78 (m), 4.31-4.34 (m), 4.55-4.58 (m), 5.66 (d, *J* = 6.3 Hz), 5.72 (d, *J* = 7.5 Hz), 6.40-6.43 (m), 6.51 (t, *J* = 3.0 Hz), 5.54 (t, *J* = 3.0 Hz), 6.75 (s), 7.09-7.12 (m), 7.21-7.34 (m), 7.44-7.50 (m), 7.53-7.58 (m), 7.64-7.71 (m), 8.06 (d, *J* = 7.5 Hz). Anal. ($C_{47}H_{54}N_4O_6S$) C, H, N.

Preparation of Product 2-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

2-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (202 mg, 0.25 mmol) was dissolved in 5 mL of dry CH_2Cl_2. Trifluoroacetic acid (4 mL) and triisopropylsilane (2 drops) were added sequentially to give a bright yellow solution. After stirring for 20 min, no yellow color remained. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (2% MeOH in CH_2Cl_2) to afford 2-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) as a white solid (0.62 g, 42%): IR (thin film) 3239, 1638, 1526, 1209 cm^{-1}; ^1H NMR (mixture of rotamers) (DMSO-d_6) δ 0.57-0.65 (m), 0.82-0.85 (m), 1.11-1.17 (m), 1.35-1.50 (m), 1.68-1.80 (m), 1.98-2.06 (m), 2.71-2.97 (m), 3.10-3.17 (m), 4.26-4.46 (m), 4.69-4.71 (m), 5.00 (t, *J* = 7.5

Hz), 5.75 (s), 6.25-6.28 (m), 6.38-6.41 (m), 6.77 (s), 7.16-7.27 (m), 7.94 (d, J = 8.1 Hz), 8.03 (d, J = 7.5 Hz), 8.26 (d, J = 7.5 Hz), 8.54 (d, 6.9 Hz). Anal. ($C_{28}H_{40}N_4O_6S{\bullet}0.75\ H_2O$) C, H, N. HRMS calcd for $C_{28}H_{40}N_4O_6S$+Cs 693.1723, found 693.1739.

Example 8 - Preparation of Compound 9: Ethyl-3-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of cyclopentylthiocarbonyl- L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminol), CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) was synthesized from CBZ-L-hPhe and L-N-Me-Phe-L-(Tr-Glutaminol) in 71% yield: white amorphous solid: IR(KBr) 3295, 3061, 3027, 2936, 1659, 1495, 1447, 1261, 1043, 750, 698 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ 0.51 (m), 1.47 (m), 1.77 (m), 2.10-2.70 (m), 2.78 (s), 2.85 (s), 2.89 (m), 3.20 (m), 3.78 (m), 3.83 (m), 4.22 (m), 4.60-5.10 (m), 7.03-7.36 (m), 7.48 (m), 7.72 (d, J = 9.0 Hz), 7.84 (d, J = 7.0 Hz), 8.49 (s), 8.51 (s). Anal. ($C_{52}H_{54}N_4O_6$) C, H, N.

Preparation of Intermediate L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of L-N-Me-Phe-L-(Tr-glutaminol), L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) was synthesized from CBZ-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) in 96% yield: white amorphous solid: IR(KBr) 3331, 3057, 3029, 2936, 1657, 1493, 1449, 752, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ (mixture of rotamers) 1.38-1.60 (m), 1.73 (m), 2.05-2.40 (m), 2.58 (m), 2.70 (s), 2.78 (s), 2.90 (m), 3.10-3.33 (m), 3.51 (m), 3.72 (m), 4.63 (m), 4.74 (m), 4.95 (m), 7.02-7.28 (m), 7.51 (d, J = 8.0 Hz), 8.50 (m), 8.55 (s). Anal. ($C_{44}H_{48}N_4O_4$) C, H, N.

Preparation of Intermediate Benzyl chlorothiolformate.

Using the procedure described in Example 4 for the preparation of cyclopentyl chlorothiolformate, benzyl chlorothiolformate was synthesized from benzylmercaptan in 71% yield: colorless liquid (bp 95-100 °C; 8 torr): IR(neat) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ

4.19 (s, 2H), 7.30-7.34 (m, 5H). This compound is reported in the literature, for example, in J.J Willard et al., *J. Am. Chem. Soc.* **1960**, *82*, 4347, the disclosure of which is entirely incorporated herein by reference.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol).

L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol) (0.62 g, 0.88 mmol) was dissolved in 7 mL of CH_2Cl_2. Benzyl chlorothiolformate (0.134 mL, 0.88 mmol) dissolved in 2 mL of CH_2Cl_2 was added dropwise followed by 0.13 mL (0.90 mmol) of Et_3N. The reaction mixture was stirred for 15 minutes at rt, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (gradient: 0-1.5% MeOH/$CHCl_3$) to give 0.70 g (94%) of a white amorphous solid: IR(KBr) 3287, 3061, 3026, 2936, 1641, 1495, 1449, 1213, 750, 698 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ 0.56 (m), 1.30-1.90 (m), 2.10-2.44 (m), 2.79 (s), 2.84 (s), 2.95 (m), 3.15 (m), 3.83 (d, J = 13.6 Hz), 3.98 (d, J = 13.6 Hz), 4.04 (m), 4.41 (m), 4.57-4.70 (m), 4.82 (m), 5.07 (m), 7.02-7.29 (m), 7.48 (d, J = 8.0 Hz), 7.64 (d, J = 8.0 Hz), 8.47 (m), 8.52 (s), 8.76 (d, J = 7.0 Hz). Anal. ($C_{52}H_{54}N_4O_5S \cdot 0.5\ H_2O$) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminal).

Using the procedure described in Example 4 for the preparation of cyclopentylthiocarbonyl- L-Leu-L-N-Me-L-Phe-L-(Tr-glutaminal), benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminol) in 75% yield and used without further purification: white amorphous solid: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ 0.60 (m), 2.20-2.49 (m), 2.81 (s), 2.84 (s), 2.95 (m), 3.24 (m), 3.80-4.05 (m), 4.17 (m), 4.42 (m), 4.59 (m), 4.95 (m), 5.24 (m), 7.03-7.29 (m), 8.29 (d, J = 9.0 Hz), 8.34 (d, J = 8.0 Hz), 8.47 (d, J = 8.0 Hz), 8.55 (s), 8.63 (s), 8.75 (d, J = 7.0 Hz), 9.26 (s), 9.39 (s).

Preparation of Intermediate Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) to give material contaminated with triphenyphosphine oxide after chromatography which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.46 (m), 1.19 (t, J = 7.0 Hz), 1.63-1.91 (m), 2.26 (m), 2.44 (m), 2.80 (s), 2.82 (s), 2.94 (m), 3.17 (m), 3.82 (d, J = 14.0 Hz), 3.97 (d, J = 13.6 Hz), 4.09 (q, J = 7.0 Hz), 4.10 (q, J = 7.0 Hz), 4.45 (m), 4.98 (m), 5.12 (m), 5.67 (d, J = 14.0 Hz), 5.93 (d, J = 15.5 Hz), 6.71 (dd, J = 16.0, 5.5 Hz), 6.83 (dd, J = 15.5, 5.0 Hz), 7.02-7.29 (m), 8.05 (m), 8.44 (d, J = 8.0 Hz), 8.54 (s), 8.62 (s), 8.84 (d, J = 6.0 Hz).

Preparation of Product - Ethyl-3-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-3-(benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate in 81% yield as a white amorphous solid (two steps from the aldehyde intermediate): mp = 64-67°C: IR(KBr) 3285, 1641, 1537, 1454, 1208, 700 cm^{-1}, ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.42 (m), 1.19 (t, J = 7.0 Hz), 1.60-2.70 (m), 2.79 (s), 2.80 (s), 2.87 (m), 3.20 (m), 3.94-4.14 (m), 4.36-4.60 (m), 4.99 (m), 5.07 (m), 5.69 (d, J = 15.5 Hz), 5.99 (d, J = 15.5 Hz), 6.72 (dd, J = 15.5, 5.5 Hz), 6.76 (bs), 6.86 (dd, J = 15.5, 5.5 Hz), 6.98-7.30 (m), 8.03 (m), 8.50 (d, J = 8.0 Hz), 8.85 (d, J = 6.0 Hz). HRMS calcd for $C_{37}H_{44}N_4O_6S$+Cs 805.2036, found 805.2054. Anal. ($C_{37}H_{44}N_4O_6S{\cdot}0.45\ CHCl_3$) C, H, N.

Example 9 - Preparation of Compound 10: 2-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Preparation of Intermediate 2-[Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 5 for the preparation of 2-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone), 2-[benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) was synthesized from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal) and (triphenylphosphoranylidene)-γ-butyrolactone to give material contaminated with triphenyphosphine oxide after column chromatography which was used without further purification: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.63 (m), 1.39 (m), 1.62-1.90 (m), 2.80 (s), 2.82 (s), 2.10-2.95 (m), 3.10-3.28 (m), 3.85-4.05 (m), 4.24-4.40 (m), 4.45 (m), 4.62 (m), 4.82 (m), 5.07 (m), 6.26 (m), 6.39 (m), 7.02-7.30 (m), 8.05 (m), 8.49 (d, J = 8.0 Hz), 8.51 (s), 8.60 (s), 8.82 (d, J = 6.0 Hz).

Preparation of Product - 2-(Benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

Using the procedure described in Example 5 for the preparation of 2-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone), 2-(benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) was synthesized in 70% overall yield based on two steps from benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-glutaminal): white amorphous solid (mp = 75-79 °C): IR(KBr) 3289, 1751, 1638, 1528, 1208, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ 0.54 (m), 1.32 (m), 1.80 (m), 2.01-2.46 (m), 2.60 (m), 2.79 (s), 2.80 (s), 2.72-2.98 (m), 3.14 (m), 4.01 (d, J = 13.6 Hz), 4.05 (s), 4.12 (d, J = 13.6 Hz), 4.30-4.57 (m), 4.62 (m), 4.82 (m), 5.01 (m), 6.27 (m), 6.40 (m), 6.77 (m), 6.98-7.30 (m), 8.02 (d, J = 8.0 Hz), 8.08 (d, J = 9.0 Hz), 8.49 (d, J = 8.0 Hz), 8.83 (d, J = 6.0 Hz). HRMS calcd for $C_{37}H_{42}N_4O_6S$+Cs 803.1879, found 803.1863. Anal. ($C_{37}H_{42}N_4O_6S$•0.35 $CHCl_3$) C, H, N.

Example 10 - Preparation of Compound 11: Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This material was prepared from ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.397 g, 0.732 mmol) and BOC-L-Leu-L-N-Me-Phe (0.287 g, 0.731 mmol) as described in Example 6 for the formation of 1-(2',3'-dihydroindol-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (after chromatography, 44% EtOAc in hexanes) as a white foam (0.412 g, 69%): IR (thin film) 3295, 1713, 1672, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.65 (d, J = 6.2 Hz), 0.66 (d, J = 6.5 Hz), 0.84 (d, J = 6.5 Hz), 0.88 (d, J = 6.5 Hz), 1.02-1.22 (m), 1.23-1.38 (m), 1.33 (s), 1.41 (s), 1.55-1.82 (m), 1.89-2.07 (m), 2.23-2.30 (m), 2.90 (s), 2.94 (s), 3.01 (dd, J = 14.6, 10.9 Hz), 3.03-3.13 (m), 3.26-3.37 (m), 3.27 (dd, J = 14.6, 3.4 Hz), 3.42-3.54 (m), 4.00-4.22 (m), 4.37-4.73 (m), 4.82-4.89 (m), 5.63-5.70 (m), 5.95 (dd, J = 15.9, 1.2 Hz), 6.23-6.28 (m), 6.66-6.75 (m), 6.79-6.89 (m), 7.09-7.34 (m), 8.14 (d, J = 8.7 Hz); Anal. ($C_{49}H_{60}N_4O_7$) C, H, N.

Preparation of Intermediate Ethyl-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.390 g, 0.477 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.063 mL, 0.60 mmol) as described in Example 6 for the formation of 2,3-dihydroindole-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe- L-(Tr-*Gln*)]-E-propenamide to give ethyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate (after chromatography, 44% EtOAc in hexanes) as a white foam (0.261 g, 68%): IR (thin film) 3295, 1708, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.61-0.75 (m), 0.92 (d, J = 6.8 Hz), 0.68 (d, J = 6.5 Hz), 0.82-0.98 (m), 0.86 (d, J = 6.5 Hz), 0.87 (d, J = 6.2 Hz), 1.04-1.43 (m), 1.51-1.84 (m), 1.88-2.08 (m), 2.21-2.32 (m), 2.66-3.53 (m), 2.86 (s), 2.89 (s), 4.08-4.24 (m), 4.28-4.53 (m), 4.54-4.68 (m), 4.83-4.89 (m), 5.65-5.76 (m), 5.74 (d, J =

15.7 Hz), 5.96 (d, $J = 15.7$ Hz), 6.35-6.40 (m), 6.75 (dd, $J = 15.7$, 5.3 Hz), 6.80-6.89 (m), 7.09-7.35 (m), 8.03 (d, $J = 7.5$ Hz); Anal. ($C_{47}H_{56}N_4O_6S$) C, H, N.

Preparation of Product Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.220 g, 0.273 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give ethyl-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate (after chromatography, 50% acetone in hexanes) as a white foam (0.111 g, 72%): IR (thin film) 3284, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.62 (d, $J = 6.5$ Hz), 0.67 (d, $J = 6.5$ Hz), 0.89 (d, $J = 6.5$ Hz), 0.93 (d, $J = 6.5$ Hz), 1.22 (t, $J = 7.2$ Hz), 1.29 (t, $J = 7.2$ Hz), 1.37-2.04 (m), 2.13-2.44 (m), 2.58-3.36 (m), 2.93 (s), 3.12 (s), 4.17 (q, $J = 7.2$ Hz), 4.19 (q, $J = 7.2$ Hz), 4.37-4.90 (m), 4.96-5.15 (m), 5.67 (d, $J = 15.6$ Hz), 6.00 (d, $J = 15.6$ Hz), 6.12 (s, bs), 6.62-6.72 (m), 6.87 (dd, $J = 15.6$, 5.9 Hz), 6.95 (bs), 7.12-7.35 (m), 7.47 (bs), 7.83 (d, $J = 7.2$ Hz); Anal. ($C_{28}H_{42}N_4S \cdot 0.5\ H_2O$) C, H, N.

<u>Example 11 - Preparation of Compound 12:</u>
<u>2-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)- E-(α-Vinyl-γ-Butyrolactone).</u>

Preparation of Intermediate BOC-L-Val-L-N-Me-Phe-OMe.

N-Me-Phe-OMe·HCl (2.0 g) was dissolved in 50 mL of CH_2Cl_2 and poured into a combination of 1N NaOH (aq. 7 mL) and sat. $NaHCO_3$ (25 mL). After mixing, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the free base of the amine as a clear colorless oil (1.69 g, 8.75 mmol). A solution of this amine and diisopropylethylamine (1.68 mL, 9.62 mmol) in 10 mL of DMF was added dropwise to a solution of BOC-L-Val (2.09 g, 9.62 mmol) and hydroxybenzotriazole-hydrate (1.30 g, 9.62 mmol) in 10 mL DMF cooled to 0 °C. 1,3-Dicyclohexylcarbodiimide (2.18 g, 10.59 mmol) was then added. The reaction mixture was stirred at 0 °C for 1 h, and then stirred at rt. for 48 h. The mixture was filtered to remove the precipitate, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with sat. $NaHCO_3$ (100 mL), dried

over Na_2SO_4, concentrated, and purified by flash column chromatography (15 % EtOAc in hexane) to give BOC-L-Val-L-N-Me-Phe-OMe as a white solid (2.56 g, 75 %). IR (thin film) 2972, 1743, 1710, 1646, 1497, 1172 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$): δ 0.34 (d, J = 6.9 Hz), 0.66 (d, J = 6.9 Hz), 0.89 (d, J = 6.9 Hz), 0.95 (d, J = 6.9 Hz), 1.41 (s), 1.87-1.98 (m), 2.92 (s), 2.94 (s), 2.99-3.01 (m), 3.37 (d, J = 5.7 Hz), 3.42 (d, J = 5.7 Hz), 3.72 (s), 3.73 (s), 4.35 (dd, J = 9.3, 6.0 Hz); 4.94-5.02 (m), 5.07 (d, J = 9.3 Hz), 5.34 (dd, J = 9.9, 3.0 Hz), 7.17-7.32 (m). Anal. ($C_{21}H_{32}N_2O_5$) C, H, N.

Preparation of Intermediate BOC-L-Val-L-N-Me-Phe.

BOC-L-Val-L-N-Me-Phe-OMe (0.396 g, 1.01 mmol) was dissolved in 10 mL of MeOH and cooled to 0 °C. A solution of 2 N NaOH (aq 4.04 mL, 8.08 mmol) was added dropwise. The reaction mixture was stirred for 2 h at rt. and poured into 10% aq $KHSO_4$ (80 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give BOC-L-Val-L-N-Me-Phe (0.38 g, quant.) which was used without purification.

Preparation of Intermediate
2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.546 g, 1.01 mmol) was deprotected and coupled with BOC-L-Val-L-N-Me-Phe (0.38 g, 1.01 mmol) using the procedure described in Example 7 for the formation of the 2-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) to give 2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) as a white foam (0.613 g, 76%): IR (thin film) 3307, 2965, 1752, 1677, 1493, 1171 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 0.68 (d, J = 8.1 Hz), 0.81 (d, J = 6.6 Hz), 0.86 (d, J = 6.9 Hz), 1.38-1.45 (m), 1.78-2.00 (m), 2.25-2.27 (m), 2.64-2.99 (m), 3.28-3.47 (m), 3.55 (s), 3.59-3.76 (m), 4.04-4.07 (m), 4.24-4.31 (m), 4.42-4.46 (m), 4.74-4.80 (m), 4.90 (d, J = 6.9 Hz), 4.94-5.03 (m), 6.27-6.31 (m), 6.46-6.49 (m), 6.84 (s), 6.96 (s), 7.02 (s), 7.12-7.33 (m), 7.46-7.49 (m), 7.53-7.55 (m), 7.64-7.70 (m), 7.93 (d, J = 8.1 Hz); Anal. ($C_{48}H_{56}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Intermediate 2-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-Vinyl-γ-Butyrolactone).

2-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) (0.376, 0.47 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.06 mL, 0.47 mmol) as described in Example 7 for the formation of 2-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) to give 2-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]- E-(α-vinyl-γ-butyrolactone) as a white foam (0.150 mg, 40%): IR (thin film) 3299, 2965, 2360, 1751, 1493, 1205 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 0.36 (d, J = 6.9 Hz), 0.54 (d, J = 6.6 Hz), 0.71 (d, J = 6.9 Hz), 0.85 (d, J = 6.3 Hz), 1.21-1.31 (m), 1.82-1.84 (m), 2.28-2.30 (m), 2.64-3.03 (m), 3.31-3.41 (m), 3.62-3.78 (m), 4.24-4.33 (m), 4.45-4.52 (m), 4.60-4.66 (m), 5.81-5.89 (m), 6.33-6.36 (m), 6.41-6.49 (m), 6.86(s), 7.06 (s), 7.11-7.33 (m), 7.46-7.50 (m), 7.54-7.55 (m), 7.64-7.70 (m), 7.79 (d, J = 7.5 Hz). Anal. ($C_{46}H_{52}N_4O_6S{\bullet}0.5\ H_2O$) C, H, N.

Preparation of Product - 2-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-(α-Vinyl-γ-Butyrolactone).

2-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-(α-vinyl-γ-butyrolactone) was deprotected using the procedure described in Example 7 for the formation of 2-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) to give 2-(ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-(α-vinyl-γ-butyrolactone) as a white solid (0.068 g, 96%): IR (thin film) 3748, 1625, 1541, 1200 cm^{-1}; ^1H NMR (mixture of rotamers) (DMSO-d_6) δ 0.27 (d, J = 6.6 Hz), 0.38 (d, J = 6.3 HZ), 0.55-0.59 (m), 0.79-0.84 (m), 1.11-1.17 (m), 1.70-1.83 (m), 1.88-1.95 (m), 1.98-2.07 (m), 2.72-3.26 (m), 4.05-4.10 (m), 4.25-4.44 (m), 4.64-4.66 (m), 5.12-5.18 (m), 5.33-5.36 (m), 6.23-6.26 (m), 6.34-6.39 (m), 6.75-6.78 (m), 7.12-7.26 (m), 7.78-7.84 (m), 8.13 (d, J = 7.5 Hz), 8.24-8.30 (m). HRMS calcd. for (M+Cs), 679.1566, found 679.1591. Anal. ($C_{27}H_{38}N_4O_6S{\bullet}0.3\ H_2O$) C,H,N.

Example 12 - Preparation of Compound 13:
Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me- (4-Me-Phe)-L-*Gln*]-E-Propenoate

Preparation of Intermediate FMOC-L-N-Me-(4-Me)-Phe.

This N-protected amino acid was prepared in approximately 80% yield from FMOC-L-(4-Me)-Phe, purchased from Neosystem Laboratories, Strasbourg, France, using the procedure described by R.M. Friedinger, et al.; *J. Org. Chem.* **1983**, *48*, 77-81, the disclosure of which is entirely incorporated by reference herein. The crude product, isolated as an oil, was used without further purification: IR (thin film) 3452, 2953, 1713, 1516, 1451, 1404, 1321, 1194, 1040, 738 cm^{-1}; ^1H NMR ($CDCl_3$) mixture of rotamers; δ 2.27 (m), 2.77 (s), 2.79 (s), 2.85 (s), 3.08-3.32 (m), 3.37-3.49 (m), 4.10-4.26 (m), 4.30-4.45 (m), 4.80-4.89 (m), 5.05 (m), 6.87 (d, J = 11.0 Hz), 6.95 (d, J = 11.0 Hz), 7.09 (m), 7.25-7.55 (m), 7.75 (d, J = 7.4 Hz). MS calcd for $C_{26}H_{25}NO_4$+Na 438, found 438.

Preparation of Intermediate FMOC-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

FMOC-L-N-Me-(4-Me)-Phe (1.90 g, 4.6 mmol) was dissolved in 12 mL of CH_2Cl_2 and 2 mL of DMF. To this solution was added N-hydroxysuccinimide (0.53 g, 4.6 mmol) was added to this solution. Stirring was continued until all the solids were dissolved. N,N'-Dicyclohexylcarbodiimide (0.95 g, 4.6 mmol) was added to the reaction mixture, and the reaction was stirred at room temperature for two hours. The mixture was then filtered into a separate flask containing L-(Tr-Glutaminol) (1.72 g, 4.6 mmol) dissolved in 15 mL of DMF, removing the N,N'-dicyclohexylurea precipitate. The reaction mixture was stirred overnight at room temperature. The solvents were removed under vacuum, and the resulting crude product was purified by flash chromatography (5% saturated anhydrous NH_3 in MeOH/ CH_2Cl_2) on silica gel to give 3.72 g (90%) of a white solid: IR (KBr) 3407, 3312, 3059, 3032, 2932, 1665, 1516, 1491, 1447, 1319, 1188, 741, 700 cm^{-1}; ^1H NMR (DMSO-d_6) mixture of rotamers; δ 1.55 (m), 1.67 (m), 2.16 (bs), 2.23 (bs), 2.79 (s), 3.00-3.29 (m), 3.75 (m), 4.01-4.10 (m), 4.25 (m), 4.50-4.64 (m), 4.85 (m), 6.98-7.39 (m), 7.49 (d, J = 7.4 Hz), 7.60-7.75 (m), 7.87 (d, 1 H, J = 7.4 Hz), 8.50 (bs). MS calcd for $C_{50}H_{49}N_3O_5$+Na 794, found 794.

Preparation of Intermediate L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

FMOC-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) (3.32 g, 4.3 mmol) was dissolved in 11 mL of DMF. Piperidine (0.44 g, 5.2 mmol) was added dropwise to this solution. The solution was stirred for 30 min. At this time, the solution was concentrated under vacuum, and the resulting crude amine was purified by flash chromatography (7% MeOH/ CH_2Cl_2) on silica gel to give 2.12 g (90%) of a white tacky foam: IR (thin film) 3302, 3057, 3025, 2934, 2865, 1956, 1925, 1809, 1659, 1516, 1265, 1035, 737, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (m, 1H), 1.89 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.37 (m, 2H), 2.67 (dd, 1H, J = 13.8, 9.0 Hz), 3.09 (dd, 1H, J = 13.4, 4.6 Hz), 3.20 (dd, 1H, J = 8.8, 4.4 Hz), 3.42 (m, 2H), 3.52 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H), 6.94 (m, 2H), 7.09 (m, 2H), 7.23-7.32 (m, 16H), 7.44 (d, 1 H, J = 7.7 Hz). MS calcd for $C_{35}H_{39}N_3O_3$+Cs 682, found 682.

Preparation of Intermediate CBZ-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Following the procedure of L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397, the disclosure of which is entirely incorporated herein by reference, CBZ-L-hPhe was coupled with L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) as follows. To CBZ-L-hPhe (0.32 g, 1.0 mmol) was added 3 mL of DMF. To this solution was added L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) (0.55 g, 1.0 mmol) and diisopropylethylamine (0.26 g, 2.0 mmol). This solution was then cooled to 0 °C, and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.38 g, 1.0 mmol) was added. The solution instantly turned yellow, and the mixture was allowed to warm to rt. Once the starting materials were consumed as indicated by TLC, the reaction mixture was concentrated under vacuum. The residue was taken up in an excess of EtOAc (200 mL), and washed with 25 mL of H_2O, 25 mL 10% HCl twice, and then 5% aq $NaHCO_3$. The organic layer was dried over anh Na_2SO_4 and concentrated. The residue was subjected to flash chromatography (5% MeOH/ CH_2Cl_2) on silica gel to give 0.68 g (80%) of a white solid: IR (KBr) 3403, 3059, 3030, 2947, 1662, 1516, 1448, 1264, 752, 700 cm^{-1}; ^1H NMR (DMSO-d_6) mixture of rotamers; δ 0.45 (m), 1.27-1.65 (m), 1.77-1.95 (m), 1.97 (s), 2.07-2.15 (m), 2.18 (s), 2.19-2.25 (m), 2.37 (m), 2.68-2.94 (m), 3.05-3.35 (m), 3.75 (m),

3.80 (m), 4.20-4.40 (m), 4.54-5.03 (m), 6.92-7.34 (m), 7.43-7.85 (m), 8.49 (m). MS calcd for $C_{53}H_{56}N_4O_6$+Cs 977, found 977.

Preparation of Intermediate L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Using the catalytic hydrogenation procedure described in Example 4 for the preparation of L-(Tr-Glutaminol), the amine was prepared in quantitative yield from CBZ-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol). White glassy solid: IR (KBr) 3378, 3057, 3027, 2938, 1659, 1516, 1493, 1447, 1180, 752, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 1.30-1.60 (m), 1.68 (m), 2.07 (m), 2.16 (s), 2.22 (m), 2.57 (m), 2.68 (s), 2.77 (s), 2.82-3.30 (m), 3.75 (m), 4.30-4.80 (m), 4.90-5.00 (m), 6.97-7.43 (m), 8.35-8.55 (m). MS calcd for $C_{45}H_{50}N_4O_4$+Na 733, found 733.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 8 for the preparation of benzylthiocarbonyl-L-hPhe-L-N-Me-Phe-L-(Tr-Glutaminol), benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminol) was prepared from L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminol) and benzyl chlorothiolformate in 96% yield. White solid: IR (KBr) 3418, 3316, 3054, 3023, 2947, 1678, 1666, 1643, 1530, 1493, 1451, 1211, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 0.55 (m), 1.25-1.60 (m), 1.80-1.93 (m), 1.96 (s), 2.19 (s), 2.22 (m), 2.40 (m), 2.68 (s), 2.72-2.96 (m), 3.17-3.27 (m), 3.40 (m), 3.65 (m), 3.80-4.10 (m), 4.54-5.03 (m), 6.84-7.29 (m), 7.47 (d, J = 8.1 Hz), 7.55 (d, J = 7.5 Hz), 7.66 (d, J = 8.4 Hz), 8.44-8.52 (m), 8.76 (d, J = 7.5 Hz). MS calcd for $C_{53}H_{56}N_4O_5S$+Na 883, found 883.

Preparation of Intermediate Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminal).

Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) was oxidized using o-iodoxybenzoic acid in anh. DMSO as described in Example 4 for the preparation of

cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal). Upon workup, the aldehyde was used immediately without further purification. ^{1}H NMR ($CDCl_3$) mixture of rotamers; δ 0.89 (m), 1.26 (m), 1.67 (m), 1.85-2.05 (m), 2.13 (s), 2.22 (m), 2.28 (s), 2.35 (m), 2.60 (m), 2.70 (s), 2.83 (s), 2.89-2.95 (m), 2.99 (s), 3.01 (m), 3.25 (m), 3.90 (m), 4.04-4.25 (m), 4.30 (m), 4.61-4.66 (m), 5.85 (d, J = 7.0 Hz), 5.95 (d, J = 7.0 Hz), 6.22 (d, J = 7.0 Hz), 6.70-7.36 (m), 8.15 (d, J = 7.0 Hz). 9.35 (s), 9.40 (s).

Preparation of Intermediate Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This intermediate was prepared from benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminal) and (carbethoxymethylene)triphenylphosphorane as described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate. White solid: IR (thin film) 3297, 3057, 3027, 2980, 2928, 1714, 1651, 1516, 1495, 1447, 1267, 1213, 1035, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) mixture of rotamers; δ 0.88 (m), 1.26 (t, J = 7.2 Hz), 1.44 (m), 1.61-1.80 (m), 1.94 (m), 2.10 (s), 2.23 (m), 2.29 (s), 2.54 (m), 2.67 (s), 2.85 (s), 2.90 (m), 2.98 (s), 3.03 (m), 3.17-3.29 (m), 3.84-4.07 (m), 4.14 (m), 4.35 (m), 4.58 (m), 5.73 (dd, J = 15.8, 1.5 Hz), 5.91-5.99 (m), 6.04 (d, J = 7.7 Hz), 6.47 (d, J = 8.5 Hz), 6.72 (dd, J = 15.5, 5.1 Hz), 6.82 (m), 6.87-7.08 (m), 7.14-7.31 (m), 7.77 (d, J = 7.0 Hz). MS calcd for $C_{57}H_{60}N_4O_6S$+Na 951, found 951.

Preparation of Product - Ethyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]- E-Propenoate.

This product was prepared in 69% overall yield (3 steps) from intermediate benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) by the deprotection of ethyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-propenoate using the procedure described in Example 4 for the synthesis of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate. White solid: IR (KBr) 3414, 3327, 3293, 3205, 3025, 2980, 2930, 1717, 1674, 1644, 1537, 1454, 1283, 1217, 1194, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) mixture of rotamers; δ 0.30 (m), 0.84 (m), 1.19 (t, J = 7.0 Hz), 1.33 (m), 1.77 (m), 1.92 (s), 2.05 (m), 2.20 (s), 2.40 (m), 2.57 (m), 2.77 (s),

2.80 (s), 2.84-2.90 (m), 3.05 (m), 3.94-4.14 (m), 4.36-4.60 (m), 5.01 (m), 5.63-5.73 (m), 6.01 (dd, J = 15.8, 1.1 Hz), 6.68-6.91 (m), 6.93-7.35 (m), 7.70 (m), 8.02 (m), 8.48 (d, J = 8.1 Hz), 8.65 (d, J = 8.0 Hz), 8.85 (d, J = 5.9 Hz). HRMS calcd for $C_{38}H_{46}N_4O_6S$+Cs 819.2192, found 819.2177. Anal. ($C_{38}H_{46}N_4O_6S$) C, H, N, S.

Example 13 - Preparation of Compound 14: Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This intermediate was prepared from benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-glutaminal) using (carbethoxyethylidene)triphenylphosphorane in place of (carbethoxymethylene)triphenylphosphorane in the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate. After column chromatography on silica gel (5% MeOH/CH_2Cl_2), two fractions were collected, one impure with triphenylphosphine oxide. (Analytical sample) White solid: IR (thin film) 3289, 3057, 3027, 2978, 2928, 1707, 1676, 1642, 1516, 1495, 1449, 1253, 1215, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) mixture of rotamers; δ 0.83 (m), 1.26 (m), 1.47-1.50 (m), 1.63-1.70 (m), 1.78 (m), 1.85 (d, J = 1.5 Hz), 1.87 (m), 1.92 (d, J = 1.5 Hz), 2.10 (s), 2.20 (m), 2.30 (s), 2.35-2.61 (m), 2.71 (s), 2.88 (s), 2.92 (m), 2.99 (s), 3.03-3.29 (m), 3.93 (d, J = 13.6 Hz), 4.06-4.23 (m), 4.35 (m), 4.52-4.69 (m), 5.94 (d, J = 7.4 Hz), 6.23 (d, J = 8.5 Hz), 6.28 (d, J = 7.7 Hz), 6.42 (dd, J = 9.0, 1.3 Hz), 6.58 (dd, J = 9.4, 1.3 Hz), 6.89 (bs), 6.92-7.17 (m), 7.20-7.33 (m), 7.64 (d, J = 7.7 Hz). MS calcd for $C_{58}H_{62}N_4O_6S$+Na 965, found 965.

Preparation of Product - Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-*Gln*]-E-Propenoate.

This product was prepared in 89% overall yield (3 steps) from intermediate benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-Glutaminol) by the deprotection of ethyl-2-methyl-3-[benzylthiocarbonyl-L-hPhe-L-N-Me-(4-Me)-Phe-L-(Tr-*Gln*)]-E-propenoate using the procedure described in Example 4 for the synthesis of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate. White solid: IR

(KBr) 3302, 3223, 2984, 2928, 1709, 1672, 1642, 1535, 1453, 1256, 1217, 1132, 700 cm^{-1}; ^1H NMR (DMSO-d_6) mixture of rotamers; δ 0.34 (m), 1.17(m), 1.30 (m), 1.72 (m), 1.78 (s), 1.87 (s), 1.93 (s), 1.97-2.04 (m), 2.19 (s), 2.40 (m), 2.59 (m), 2.77 (s), 2.79 (s), 2.83 (m), 3.05 (m), 4.07 (m), 4.39 (m), 4.64 (m), 4.85 (m), 4.91 (m), 6.40 (d, J = 9.6 Hz), 6.54 (d, J = 8.5, 1.1 Hz), 6.74 (m), 6.76-7.30 (m), 7.99 (d, J = 8.1 Hz), 8.47 (d, J = 6.6 Hz), 8.84 (d, J = 6.3 Hz). HRMS calcd for $C_{39}H_{48}N_4O_6S$+Cs 833.2349, found 833.2329. Anal. ($C_{39}H_{48}N_4O_6S$) C, H, N, S.

Example 14 - Preparation of Compound 15: Ethyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me- Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-OMe.

To 2-isocyanato-4-methylvaleric acid methyl ester (0.86 g, 5.0 mmol) dissolved in 50 mL of THF was added benzyl mercaptan (0.59 mL, 5.0 mmol). The reaction mixture was stirred at rt overnight, and the solvent was removed in vacuo to give a yellow liquid which was purified by flash column chromatography on silica gel (gradient; 5-10% of EtOAc/hexanes) to give 1.39 g (94%) of benzylthiocarbonyl-L-Leu-OMe as a clear oil: IR (neat) 3320, 2957, 1746, 1651, 1520, 1454, 1200, 839, 702 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.97 (m, 6H), 1.65 (m, 3H), 3.74 (s, 3H), 4.16 (s, 2H), 4.60 (m, 1H), 5.72 (d, 1H, J = 8.0 Hz), 7.32 (m, 5H). Anal. ($C_{15}H_{21}NO_3S$) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu.

Benzylthiocarbonyl-L-Leu-OMe (0.85 g, 2.88 mmol) was dissolved in 30 mL of THF. To this solution was added 1N LiOH (3.0 mL, 3.0 mmol), and the reaction mixture was stirred at rt overnight. At this time an additional 1.5 mL of 1N LiOH was added, and the reaction mixture was further stirred for 4 h. At this time, an additional 1.5 mL of 1N LiOH was added. After another 3 h at room temperature, the pH was adjusted to 7 with 10% HCl, and the THF was removed in vacuo. The aqueous phase was washed with Et_2O and separated, then adjusted to pH 1-2. The product was extracted with CH_2Cl_2, and the organic phase washed with brine, dried over $MgSO_4$, filtered, and then concentrated to give 0.29 g of benzylthiocarbonyl-L-Leu as a clear liquid that was contaminated with benzyl mercaptan: ^1H NMR (DMSO-d_6) δ 0.83 (d, 3H, J = 6.0 Hz), 0.87 (d, 3H, J = 6.0 Hz),

1.45 (m, 3H), 4.04 (s, 2H), 4.22 (m, 1H), 7.27 (m, 5H), 8.46 (d, 1H, *J* = 7.0 Hz). MS calcd for $C_{14}H_{19}NO_3S$+H 282, found 282.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminol).

Using the procedure described in Example 4 for the preparation of cyclopenylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol), benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) was synthesized from L-N-Me-Phe-L-(Tr-glutaminol) and benzylthiocarbonyl-L-Leu in 58% yield: white amorphous solid: IR(KBr) 3289, 3057, 3027, 2953, 1638, 1493, 1449, 1206, 700 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.19 (m), 0.60 (m), 0.79 (d, *J* = 6.2 Hz), 0.80 (d, *J* = 6.2 Hz), 1.12-1.77 (m), 2.12-2.36 (m), 2.84 (s), 2.90 (m), 2.96 (s), 3.12-3.40 (m), 3.63 (m), 3.84 (d, *J* = 13.6 Hz), 3.96 (d, *J* = 13.6 Hz), 4.02 (s), 4.33 (m), 4.66 (m), 5.06 (m), 7.10-7.28 (m), 7.47 (d, J = 9 Hz), 7.61 (d, *J* = 8.5 Hz), 8.35 (d, *J* = 7.0 Hz), 8.51 (s), 8.56 (d, *J* = 7.0 Hz). Anal. ($C_{48}H_{54}N_4O_5S$) C, H, N.

Preparation of Intermediate Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-Glutaminal).

Using the procedure described in Example 4 for the preparation of cyclopenylthiocarbonyl- L-Leu-L-N-Me-Phe-L-(Tr-glutaminal), benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminol) in 93% yield and was used without further purification: white amorphous solid: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ 0.02 (m), 0.61 (d, *J* = 6.6 Hz), 0.64 (d, *J* = 6.6 Hz), 0.81 (d, *J* = 6.2 Hz), 1.05-1.75 (m), 1.98 (m), 2.23-2.48 (m), 2.84 (s), 2.93 (m), 2.96 (s), 3.23 (m), 3.84 (d, *J* = 13.6 Hz), 3.95 (d, *J* = 14.0 Hz), 4.01 (m), 4.12 (m), 4.42 (m), 4.71 (m), 4.83 (m), 5.18 (m), 7.11-7.28 (m), 8.27 (d, *J* = 8.0 Hz), 8.31 (m), 8.57 (m), 8.62 (s), 9.27 (s), 9.40 (s).

Preparation of Intermediate
Ethyl-3-[Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-Tr-*Gln*)]- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) to give 0.30 g of material contaminated with triphenylphosphine oxide after chromatography which was used without further purification: white amorphous solid: ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.12 (m), 0.86 (d, J = 6.2 Hz), 0.87 (d, J = 6.2 Hz), 1.23 (t, J = 7.0 Hz), 1.26 (t, J = 7.0 Hz), 1.49 (m), 1.72 (m), 2.10-2.45 (m), 2.88 (s), 2.96 (m), 3.03 (s), 3.17 (m), 3.83 (d, J = 13.6 Hz), 3.96 (d, J = 13.6 Hz), 4.03 (s), 4.08 (m), 4.39 (m), 4.50 (m), 4.66 (m), 4.81 (m), 5.08 (m), 5.72 (d, J = 16.0 Hz), 6.01 (d, J = 15.8 Hz), 6.77 (dd, J = 15.6, 6.0 Hz), 6.89 (dd, J = 15.8, 6.0 Hz), 7.16-7.34 (m), 8.09 (d, J = 8.0 Hz), 8.43 (d, J = 8.0 Hz), 8.63 (s), 8.68 (s), 8.70 (d, J = 7.0 Hz).

Preparation of Product Ethyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)-E-propenoate in 41% yield (two steps from the aldehyde intermediate): white amorphous solid: mp = 60-63 °C): IR(KBr) 3289, 2957, 1638, 1533, 1453, 1277, 1209, 700 cm^{-1}; ^1H NMR (DMSO-d_6) (mixture of rotamers) δ -0.26 (m), 0.60 (m), 0.83 (d, J = 6.2 Hz), 1.17 (t, J = 7.0 Hz), 1.20 (t, J = 7.0 Hz), 1.03-1.60 (m), 1.66-1.98 (m), 2.01 (m), 2.80 (s), 2.92 (m), 2.96 (s), 3.25 (m), 3.92-4.18 (m), 4.38 (m), 4.48 (m), 4.68 (m), 4.86 (m), 5.08 (m), 5.69 (d, J = 16.0 Hz), 5.99 (d, J = 16.0 Hz), 6.69-6.76 (m), 6.86 (dd, J = 16.0, 6.0 Hz), 7.14-7.29 (m), 8.00 (m), 8.36 (d, J = 8.5 Hz), 8.64 (d, J = 6.6 Hz). HRMS calcd for $C_{33}H_{44}N_4O_6S$+Cs 757.2036, found 757.2008. Anal. ($C_{33}H_{44}N_4O_6S$) C, H, N.

Example 15 - Preparation of Compound 16: Ethyl-2-Methyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate
Ethyl-2-Methyl-3-[Benzylthiocarbonyl-L-Leu-L-N-Me-Phe- L-(Tr-*Gln*)]-E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, ethyl-2-methyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate was synthesized from benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-glutaminal) (0.2 g, 0.25 mmol) and (carbethoxyethylidene) triphenylphosphorane (0.11 g, 0.3 mmol) in 5 mL THF to give 0.12 g of material contaminated with triphenylphosphine oxide after column chromatography on silica gel (gradient; 0-1% MeOH/$CHCl_3$) which was used without further purification. White amorphous solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -.012 (m), 0.61 (m), 0.80 (d, J = 6.2 Hz), 1.10-1.34 (m), 1.38-1.74 (m), 1.76 (s), 1.81 (s), 2.10-2.48 (m), 2.83 (s), 2.94 (s), 3.13 (m), 3.85 (d, J = 14.0 Hz), 3.98 (d, J = 14.0 Hz), 4.02 (s), 4.09 (m), 4.35 (m), 4.57 (m), 4.73 (m), 4.97 (m), 6.38 (d, J = 10.0 Hz), 6.53 (d, J = 9.0 Hz), 7.10-7.28 (m), 7.98 (m), 8.35 (d, J = 8.0 Hz), 8.51 (s), 8.58 (s), 8.63 (d, J = 6.0 Hz).

Preparation of Product
Ethyl-2-Methyl-3-(Benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)- E-Propenoate.

Using the procedure described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate, ethyl-2-methyl-3-(benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate was synthesized from ethyl-2-methyl-3-[benzylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate in 24% yield (two steps from the aldehyde intermediate). White amorphous solid: ^{1}H NMR (DMSO-d_6) (mixture of rotamers) δ -0.16 (m), 0.59 (m), 0.84 (m), 1.08-1.83 (m), 1.78 (s), 1.86 (s), 2.03 (m), 2.79 (s), 2.94 (s), 3.16 (m), 3.97-4.21 (m), 4.35 (m), 4.53-4.78 (m), 5.08 (m), 6.39 (d, J = 9.0 Hz), 6.55 (d, J = 9.0 Hz), 6.82 (m), 7.12-7.29 (m), 7.96 (m), 8.35 (d, J = 6.6 Hz), 8.65 (d, J = 7.0 Hz). HRMS calcd for $C_{34}H_{46}N_4O_6S$+Cs 771.2192, found 771.2172. Anal. ($C_{34}H_{46}N_4O_6S$) C, H, N.

Example 16 - Preparation of Compound 17: 1-[2'-Oxazolidon-3'-yl]-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenone.

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-Propenone.

To 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (1.0 g, 1.94 mmol) in 12.0 mL of anh THF was added triethylamine (0.68 mL, 4.86 mmol). The mixture was cooled to -20 °C and pivaloyl chloride (0.24 mL, 1.94 mmol) was added. The reaction mixture was stirred at -20 °C for 2.5 h, at which time solid lithium chloride (0.091 g, 2.14 mmol) and 2-oxazolidone (0.17 g, 1.94 mmol) were added. The reaction mixture was allowed to warm to rt and further stirred overnight. The mixture was then concentrated to dryness, and the residue was taken up in CH_2Cl_2 and washed with 5% $KHSO_4$. The organic layer was separated, and the aqueous layer was reextracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to yield 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.61 g, 54 %) as an off-white solid foam. ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 4.5 H), 1.43 (s, 4.5 H), 1.81 (m, 1H), 1.98 (m, 1H), 2.40 (t, 2H, J = 7.2 Hz), 4.02-4.08 (m, 2H), 4.37-4.44 (m, 3H), 4.88 (d, 1H, J = 8.1 Hz), 6.87 (bs, 1H), 6.99 (dd, 1H, J = 15.8, 5.2 Hz), 7.18-7.32 (m, 16H). MS calcd for $C_{34}H_{37}N_3O_6$+H 584, found 584.

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]- E-Propenone.

To 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-(Tr-*Gln*)]-E-propenone (0.60 g, 1.02 mmol) dissolved in isopropyl alcohol (17.25 mL), $HClO_4$ (5.0 mL, 79.63 mmol) was added, and the reaction mixture was stirred at rt for 1.5 h. The mixture was then poured into an aq solution of 1N NaOH (3.0 mL) along with a sat. $NaHCO_3$ solution (30.0 mL) and was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated to give the free amine (0.46 g, 0.96 mmol), which was coupled immediately with BOC-L-Leu-L-N-Me-Phe (0.38 g, 0.96 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]- E-propenoate to provide 1-[2'-oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]- E-propenone (0.33 g, 41 %) as a tan solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR

$(CDCl_3)$ δ 0.65 (t, J = 6.8 Hz), 0.72 (m), 0.84-0.89 (m), 1.07 (m), 1.24-1.44 (m), 1.63 (m), 1.84 (m), 2.08 (m), 2.28-2.36 (m), 2.90 (s), 3.01 (m), 3.34 (m, 4.01-4.06 (m), 4.16 (m), 4.38-4.42 (m), 4.64 (m), 4.73 (m), 4.85 (m), 6.76 (bs), 7.04 (dd, J = 15.5, 6.1 Hz), 7.12-7.41 (m), 8.29 (d, J = 8.4 Hz). MS calcd for $C_{50}H_{59}N_5O_8$+H 858, found 858.

Preparation of Intermediate 1-[2'-Oxazolidon-3'-yl]-3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-Propenone.

1-[2'-Oxazolidon-3'-yl]-3-[BOC-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-propenone (0.32 g, 0.37 mmol) was deprotected with $HClO_4$ using the procedure described in the previous preparation and was subsequently coupled to ethylchlorothiolformate (0.042 mL, 0.40 mmol) using the procedure described in Example 6 for the preparation of 2,3-dihydroindole-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide to provide 1-[2'-oxazolidon-3'-yl]-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]-E-propenone (0.22 g, 78 %) as an off-white solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR $(CDCl_3)$ δ 0.62-0.76 (m), 0.85-0.87 (m), 1.13-1.26 (m), 1.37 (m), 1.62 (m), 1.85 (m), 2.06 (m), 2.58-2.72 (m), 2.67-2.89 (m), 3.18-3.40 (m), 4.02-4.07 (m), 4.39-4.44 (m), 4.64-4.67 (m), 5.71 (m), 6.76 (bs), 7.00 (m), 7.14-7.35 (m), 8.06 (d, J = 8.4 Hz). MS calcd for $C_{48}H_{55}N_5O_7S$+Cs 978, found 978.

Preparation of Product - 1-[2'-Oxazolidon-3'-yl]-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-Propenone.

1-[2'-Oxazolidon-3'-yl]-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-(Tr-*Gln*)]- E-propenone (0.22 g, 0.26 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide 1-[2'-oxazolidon-3'-yl]-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-*Gln*)-E-propenone (0.056 g, 35 %) as a white solid: mp = 110-111 °C; IR (thin film) 3272, 1677 cm^{-1}; ^{1}H NMR $(CDCl_3)$ δ 0.64-0.70 (m), 0.89-0.91 (m), 1.19-1.28 (m), 1.40 (m), 1.65 (m), 2.03 (m), 2.23-2.25 (m), 2.76-2.96 (m), 3.48 (q, J = 7.2 Hz), 4.04-4.10 (m), 4.41-4.46 (m), 4.65-4.67 (m), 5.48 (m), 6.12 (m), 6.24 (bs), 7.02 (m), 7.15-7.36 (m), 7.91 (m). HRMS calcd for $C_{29}H_{41}N_5O_7S$+Cs 736.1780, found 736.1803; Anal ($C_{29}H_{41}N_5O_7S$) C, H, N.

Example 17 - Preparation of Compound 18:
Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]- E-Propenoate.

Preparation of Intermediate BOC-L-(3R-Phenyl)-Pro.

(2S, 3R)-3-Phenylpyrrolidine-2-carboxylic acid (0.10 g, 0.52 mmol) was suspended in 1,4-dioxane and 800 mL of 1N NaOH was added to form a clear solution. Di-*tert*-butyl dicarbonate (0.13 g, 0.58 mmol) was added over a period of 30 minutes, and the reaction mixture was stirred overnight at rt. At this time, the reaction mixture was concentrated in vacuo, and the resulting residue was taken up in a saturated solution of $NaHCO_3$. This solution was washed with ether, and the aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic phase was separated and dried over $MgSO_4$ and concentrated to provide BOC-L-(3R-phenyl)-Pro (0.15 g, 97%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.03 (m, 1H), 2.35 (m, 1H), 3.49-3.83 (m, 4H), 7.33-7.35 (m, 5H). MS calcd for $C_{16}H_{21}NO_4$+H 292, found 292.

Preparation of Intermediate
Ethyl-3-[BOC-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.28 g, 0.52 mmol) was deprotected and coupled to BOC-L-(3R-phenyl)-Pro using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 73%) as a white glassy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.25-1.31 (m, 3H), 1.40 (bs, 9H), 2.03 (m, 2H), 2.41 (m, 2H), 3.48 (m, 2H), 3.67 (m, 2H), 4.14-4.21 (m, 4H), 4.68 (m, 1H), 5.62 (d, 1H, J = 16.5 Hz), 6.32 (m, 1H), 6.75 (dd, 1H, J = 15.9, 5.0 Hz), 6.96 (s, bs, 1H), 7.20 - 7.33 (m, 20H). MS calcd for $C_{44}H_{49}N_3O_6$+H 716, found 716.

Preparation of Intermediate - Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate was deprotected and coupled to CBZ-Leu (0.10 g, 0.37 mmol) using the procedure described in Example 1 for the

preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.19 g, 60%) as a white glassy solid. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 6.5 Hz), 0.93 (d, 3H, *J* = 6.5 Hz), 1.94 (m, 1H), 1.29 (t, 3H, *J* = 7.2 Hz), 1.34 - 1.51 (m, 2H), 2.07 (m, 1H), 2.23 (m, 1H), 2.37 (m, 1H), 2.44 - 2.48 (m, 2H), 3.50-3.52 (m, 2H), 3.67-3.69 (m, 2H), 4.04 - 4.19 (m, 4H), 4.45-4.52 (m, 2H), 4.80 (d, 1H, *J* = 9.0 Hz), 5.05 (d, 1H, *J* = 12.1 Hz), 5.12 (d, 1H, *J* = 12.1 Hz), 5.44 (dd, 1H, *J* = 15.6, 1.9 Hz), 5.65 (d, 1H, *J* = 8.7 Hz), 6.66 (dd, 1H, *J* = 15.7, 4.5 Hz), 7.17-7.38 (m, 25H); MS calcd for $C_{53}H_{58}N_4O_7$+H 863, found 863.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenoate was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)- E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-*Gln*]-E-propenoate (0.098 g, 70%) as a white solid after column chromatography on silica (5% methanol/$CHCl_3$). mp = 72-75 °C; IR (thin film) 3311, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.0 Hz), 1.44-1.57 (m, 4H), 1.75 (m, 1H), 2.10 (m, 1H), 2.17-2.28 (m, 2H), 2.34-2.43 (m, 2H), 3.51 (m, 1H), 3.73 (m, 1H), 4.13-4.20 (m, 3H), 4.59-4.66 (m, 2H), 5.11 (bs, 2H), 5.25 (bs, 1H), 5.37-5.47 (m, 2H), 5.71 (d, 1H, *J* = 9.0 Hz), 6.57 (bs, 1H), 6.70 (dd, 1H, *J* = 15.7, 4.5 Hz), 7.25-7.41 (m, 10H). HRMS calcd for $C_{34}H_{44}N_4O_7$+Cs 753.2264, found 753.2240. Anal ($C_{34}H_{44}N_4O_7$) C, H, N.

<u>Example 18 - Preparation of Compound 19: Ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.</u>

Preparation of Intermediate Ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 0.55 mmol) was deprotected and coupled to BOC-L-Pro (0.11 g, 0.55 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 85%) as a white glassy solid after column chromatography on silica (5% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*

= 7.2 Hz), 1.43 (bs, 10H), 1.82-2.00 (m, 6H), 2.34 (t, 2H, *J* = 7.2 Hz), 3.34 (m, 2H), 4.14-4.21 (m, 3H), 4.62 (m, 1H), 5.92 (dd, 1H, *J* = 15.6, 1.5 Hz), 6.80 (dd, 1H, *J* = 15.7, 5.1 Hz), 7.18-7.33 (m, 16H). MS calcd for $C_{38}H_{45}N_3O_6$+Cs 772, found 772.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.30 g, 0.47 mmol) was deprotected and coupled with CBZ-Leu (0.12 g, 0.47 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 64%) as a white foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 6.5 Hz), 0.92 (d, 3H, *J* = 6.2 Hz), 1.27 (t, 3H, *J* = 7.0 Hz) 1.35 (m, 1H), 1.63-1.75 (m, 2H), 1.99-2.10 (m, 5H), 2.39 (m, 2H), 3.53 (m, 1H), 3.73-3.76 (m, 3H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.26 (m, 1H), 4.49-4.51 (m, 3H), 5.02-5.12 (m, 3H), 5.85 (dd, 1H, *J* = 15.9, 1.6 Hz), 6.78 (dd, 1H, *J* = 15.7, 5.1 Hz), 7.07 (bs, 1H), 7.19-7.33 (m, 20H). MS calcd for $C_{47}H_{54}N_4O_7$+Cs 919, found 919.

Preparation of Product - Ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.22 g, 0.28 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe- L-*Gln*)-E-propenoate, to provide ethyl-3-(CBZ-L-Leu-L-Pro-L-*Gln*)-E-propenoate (0.092 g, 61%) as a white solid after preparative TLC (10% methanol/$CHCl_3$): mp = 55-60 °C; IR (thin film) 3300, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J* = 6.5 Hz), 0.98 (d, 3H, *J* = 6.5 Hz) 1.28 (t, 3H, *J* = 7.2 Hz), 1.46 (t, 2H, *J* = 7.0 Hz), 1.70-1.75 (m, 2H), 2.03-2.33 (m, 7H), 3.60 (m, 1H), 3.79 (m, 1H), 4.19 (q, 2H, *J* = 7.2 Hz), 4.41 (m, 1H), 4.54-4.65 (m, 2H), 5.08 (dd, 2H, *J* = 15.4, 12.3 Hz), 5.54 (m, 1H), 5.44 (d, 1H, *J* = 8.4 Hz), 5.91 (dd, 1H, *J* = 15.7, 1.4 Hz), 6.36 (m, 1H), 6.77 (d, 1H, *J* = 8.7 Hz), 6.84 (dd, 1H, *J* = 15.9, 5.0 Hz), 7.34 (bs, 5H). HRMS calcd for $C_{28}H_{40}N_4O_7$+Cs 677.1951, found 677.1972. Anal ($C_{28}H_{40}N_4O_7$•$0.5H_2O$) C, H, N.

Example 19 - Preparation of Compound 20: Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-(4R-Benzyloxy)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.50 g, 0.92 mmol) was deprotected and coupled to BOC-L-(4R-benzyloxy)-Pro (0.30 g, 0.92 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[BOC-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.54 g, 78%) as a white foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.16 Hz), 1.39 (bs, 10H), 1.80 (m, 1H), 1.80 (m, 1H), 2.16 (m, 1H), 2.32 - 2.39 (m, 2H), 3.46-3.51 (m, 2H), 4.18 (q, 2H, J = 7.2 Hz), 4.26-4.35 (m, 2H), 4.46-4.49 (m, 2H), 4.56-4.66 (m, 2H), 5.90 (dd, 1H, J = 15.7 Hz), 6.80 (dd, 1H, J = 15.6, 4.8 Hz), 6.97 (m, 1H), 7.18-7.37 (m, 20H). MS calcd for $C_{45}H_{51}N_3O_7$+H 746, found 746.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.49 g, 0.72 mmol) was deprotected and coupled to CBZ-Leu (0.19 g, 0.72 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.47 g, 72%) as a white foamy solid after column chromatography on silica (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 6.5 Hz), 1.29-1.35 (m, 4H), 1.75 (m, 1H), 2.45 (m, 1H), 2.19-2.23 (m, 2H), 2.40-2.46 (m, 2H), 3.60 (m, 1H), 3.87 (m, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.27-4.37 (m, 2H), 4.48-4.54 (m, 5H), 4.97-5.09 (m, 4H), 5.83 (dd, 1H, J = 15.7, 1.7 Hz), 6.673 (d, 1H, J = 7.5 Hz), 6.78 (dd, 1H, J = 15.7, 5.1 Hz), 7.09 (bs, 1H), 7.15-7.36 (m, 25H). MS calcd for $C_{54}H_{60}N_4O_8$+H 893, observed 893.

Preparation of Product -
Ethyl-3-[CBZ-L-Leu-L-(4R-Benzyloxy)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.47 g, 0.52 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(4R-benzyloxy)-Pro-L-*Gln*]-E-propenoate (0.27 g, 81%) as a white foamy solid after column chromatography on silica (5% methanol/$CHCl_3$). IR (thin film) 3296, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90- 0.96 (m, 6H), 1.28 (t, 3H, J = 7.0 Hz), 1.44-1.46 (m, 2H), 1.69-1.71 (m, 2H), 2.07-2.37 (m, 5H), 3.67 (dd, 1H, J = 10.7, 4.5 Hz), 4.03 (d, 1H, J = 10.9 Hz), 4.16 (d, 1H, J = 7.2 Hz), 4.21 (d, 1H, J = 7.2 Hz), 4.32 (m, 1H), 4.46-4.55 (m, 4H), 4.62 (m, 1H), 5.02 (d, 1H, J = 12.3 Hz), 5.09 (d, 1H, J = 12.3 Hz), 5.31 (m, 1H), 5.46 (d, 1H, J = 9.0 Hz), 5.89 (dd, 1H, J = 15.9, 1.6 Hz), 6.43 (m, 1H), 6.65 (d, 1H, J = 9.0 Hz), 6.83 (dd, 1H, J = 15.7, 5.1 Hz), 7.33 (bs, 10H). HRMS calcd for $C_{35}H_{46}N_4O_8$+Cs 783.2370, found 783.2390; Anal ($C_{35}H_{46}N_4O_8$•0.5 H_2O) C, H, N.

Example 20 - Preparation of Compound 21: Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-*Gln*]- E-Propenoate.

Preparation of Intermediate BOC-L-(3S-Methyl)-Pro.

(2S, 3S)-3-Methyl pyrrolidine-2-carboxylic acid (0.25 g, 1.94 mmol) was protected with a BOC group following the procedure described in Example 17 for the preparation of BOC-L-(3R-Phenyl)-Pro to provide BOC-L-(3S-methyl)-Pro (0.43 g, 98%) as a white solid. ^1H NMR ($CDCl_3$) δ 1.16-1.21 (m, 6H), 1.42 (s, 9H), 1.48 (s, 9H), 1.52-1.61 (m, 2H), 2.01-2.12 (m, 2H), 2.41 (m, 1H), 2.61 (m, 1H), 3.41-3.62 (m, 4H), 3.77 (m, 1H), 3.90 (m, 1H). MS calcd for $C_{11}H_{19}NO_4$+H, 230, found 230.

Preparation of Intermediate Ethyl-3-[BOC-L-(3S-Methyl)-Pro-L-(Tr-*Gln*)] -E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.53 g, 0.97 mmol) was deprotected and coupled to BOC-L-(3S-methyl)-Pro (0.22 g, 0.97 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[BOC-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 43%) as a glassy off-white solid foam after column chromatography on silica (5% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.10-1.17 (m, 3H), 1.27 (t, 3H, J = 7.2 Hz), 1.41 (bs, 10H), 1.58 (bs, 2H), 1.80 (m, 1H), 2.00 (m, 1H), 2.36 (m, 2H), 3.30 (m, 1H), 3.40-3.66 (m, 2H), 3.70 (d, 1H, J = 5.0 Hz), 4.14-4.21 (m, 2H), 4.64 (m, 1H), 5.92 (d, 1H, J = 15.9 Hz), 6.78-6.84 (m, 2H), 7.19-7.29 (m, 15H). MS calcd for $C_{39}H_{47}N_3O_6$+H, 654, found 654.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.27 g, 0.42 mmol) was deprotected and coupled to CBZ-Leu (0.11 g, 0.42 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 52%) as a white solid foam after column chromatography on silica (4% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.2 Hz), 0.92 (d, 3H, J = 6.2 Hz), 1.10 (d, 3H, J = 7.2 Hz), 1.34 (m, 1H), 1.60-1.74 (m, 2H), 2.04-2.17 (m, 3H), 2.38-2.48 (m, 3H), 3.53 (m, 1H), 3.68 (d, 1H, J = 6.2 Hz), 3.91 (m, 1H), 4.17 (dd, 2H, J = 14.9, 6.8 Hz), 4.48-4.52 (m, 2H), 4.96-5.12 (m, 4H), 5.84 (d, 1H, J = 15.6 Hz), 6.49 (d, 1H, J = 8.1 Hz), 6.79 (dd, 1H, J = 16.2, 4.7 Hz), 7.13 (bs, 1H), 7.19-7.33 (m, 20H). MS calcd for $C_{48}H_{56}N_4O_7$+H, 801, found 801.

Preparation of Product - Ethyl-3-[CBZ-L-Leu-L-(3S-Methyl)-Pro-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 0.22 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-L-(3S-methyl)-Pro-L-*Gln*]-E-propenoate (0.078 g, 64%) as a white solid foam after column

chromatography on silica (4% methanol/$CHCl_3$). IR (thin film) 3392, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92–0.98 (m, 6H), 1.17 (d, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.41–1.49 (m, 2H), 1.64–1.76 (m, 3H), 2.10–2.28 (m, 3H), 2.35–2.48 (m, 2H), 3.59 (m, 1H), 3.85 (d, 1H, J = 6.5 Hz), 3.96 (m, 1H), 4.19 (dd, 1H, J = 14.3, 7.2 Hz), 4.54 (m, 1H), 4.68 (m, 1H), 5.04–5.13 (m, 2H), 5.31 (d, 1H, J = 9.0 Hz), 5.91 (dd, 1H, J = 15.6, 1.6 Hz), 6.51–6.54 (m, 2H), 6.85 (dd, 1H, J = 15.7, 5.1 Hz), 7.34 (bs, 5H). HRMS calcd for $C_{29}H_{42}N_4O_7$+Na, 581.2951, found 581.2937. Anal ($C_{29}H_{42}N_4O_7$•0.5 H_2O) C, H, N.

Example 21 - Preparation of Compound 22: N-Methoxy, N-Methyl-3-[CBZ-L-Leu L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenamide.

Preparation of Intermediate 3-[BOC-L-(Tr-*Gln*)]-E-Propenoic Acid.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (1.874 g, 3.46 mmol) was taken up in 20 mL EtOH, and 1N aq NaOH (7.95 mL, 7.95 mmol) was added dropwise via an addition funnel over 2 h. The resulting solution was stirred at room temperature for 1.5 h, whereupon the reaction mixture was poured into water and washed with ether. The aqueous layer was acidified to pH 3 with 1N HCl, and extracted 3 times with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated to provide 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (1.373 g, 77%) as a glassy off-white solid. No further purification was needed: IR (KBr) 3315, 1698, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.76 (m, 1H), 1.83–1.98 (m, 1H), 2.37 (t, 2H, J = 7.0 Hz), 4.30 (m, 1H), 4.88 (m, 1H), 5.85 (d, 1H, J = 15.3 Hz), 6.86 (dd, 1H, J = 15.5, 5.1 Hz), 6.92 (s, 1H), 7.25 (m, 15H).

Preparation of Intermediate N-Methoxy-N-Methyl-3-[BOC-L-(Tr-*Gln*)]-E-Propenamide.

This intermediate was prepared from 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid and *N*, *O*-dimethylhydroxylamine hydrochloride as described in Example 1 for the synthesis of intermediate BOC-L-(Tr-*Gln*)-N(OMe)Me. This intermediate can alternatively be prepared by the reaction of BOC-L-(Tr-glutaminal) with N-methoxyl-N-methyl-(2-triphenylphosphoranylidene)-acetamide in THF as described for the preparation of ethyl-3-[cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, or by the reaction of BOC-L-(Tr-glutaminal) with the anion of diethyl

(N-methoxy-N-methylcarbamoylmethyl)phosphonate as described in Example 6 for the preparation of 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-(Tr-*Gln*)]-E-propenone. IR (thin film) 3307, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.80 (m, 1H), 1.95 (m, 1H), 2.36–2.40 (m, 2H), 3.24 (s, 3H), 3.67 (s, 3H), 4.31 (m, 1H), 4.83 (m, 1H), 6.48 (d, 1H, J = 15.6 Hz), 6.79 (dd, 1H, J = 15.6, 5.6 Hz), 6.92 (m, 1H), 7.19–7.32 (m, 15H). HRMS calcd for $C_{33}H_{39}N_3O_5$+Cs, 690.1944, found 690.1967.

Preparation of Intermediate N-Methoxy-N-Methyl-3-[BOC-L-(3R-Phenyl)-Pro-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(Tr-*Gln*)]-E-propenamide (0.24 g, 0.49 mmol) was deprotected and coupled to BOC-L-(3R-phenyl)-Pro (0.14 g, 0.49 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide N-methoxy-N-methyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.22 g, 63%) as a white solid foam after column chromatography on silica (3% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.48 (m, 1H), 1.73 (m, 1H), 1.91–2.02 (m, 2H), 2.25 (m, 1H), 2.35–2.45 (m, 2H), 3.22 (s, 3H), 3.43–3.46 (m, 2H), 3.61–3.72 (m, 4H), 4.20 (m, 1H), 4.70 (m, 1H), 6.44 (m, 1H), 6.74 (m, 1H), 6.99 (m, 1H), 7.16 – 7.33 (m, 20H). MS calcd for $C_{44}H_{50}N_4O_6$+Na 753, found 753.

Preparation of Intermediate N-Methoxy-N-Methyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide(0.18g,0.26 mmol) was deprotected and coupled to CBZ-L-Leu (0.070 g, 0.26 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide N-methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.076 g, 33%) as a clear glass after column chromatography on silica (3% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.79–0.93 (m, 6H), 1.01 (m, 1H), 1.22 (m, 1H), 1.40 (m, 1H), 1.51–1.95 (m, 2H), 2.01 (m, 1H), 2.19 (m, 1H), 2.31–2.52 (m, 2H), 3.15–3.20 (m, 3H). 3.53–3.68 (m, 6H), 3.92 (m, 1H), 4.08 (m, 1H), 4.57 (m, 1H), 5.02–5.15 (m, 2H),

6.25–6.35 (m, 2H), 6.63 (m, 1H), 7.15–7.35 (m, 25H). MS calcd for $C_{53}H_{59}N_5O_7$+H 878, found 878.

Preparation of Product - N-Methoxy-N-Methyl-3-[CBZ-L-Leu-L-(3R-Phenyl)-Pro-L-*Gln*]-E-Propenamide.

N-Methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-(Tr-*Gln*)]-E-propenamide (0.076 g, 0.090 mmol) was deprotected using the procedure described in Example 1 for the synthesis of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide N-methoxy-N-methyl-3-[CBZ-L-Leu-L-(3R-phenyl)-Pro-L-*Gln*]-E-propenamide (12.0 mg, 21%) as a clear glass after column chromatography (5% methanol/$CHCl_3$). IR (thin film) 3290, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.7 Hz), 1.44–1.74 (m, 3H), 2.05 (m, 1H), 2.15–2.22 (m, 2H), 2.32 (m, 1H), 2.41 (m, 1H), 3.21 (m, 1H), 3.51–3.74 (m, 5H), 4.14 (m, 1H), 4.23 (m, 1H), 4.62–4.66 (m, 2H), 5.09–5.10 (m, 2H), 5.27 (m, 1H), 5.48 (d, 1H, J = 13.8 Hz), 6.17 (d, 1H, J = 9.0 Hz), 6.36 (d, 1H, J = 15.3 Hz), 6.59 (m, 1H), 6.65 (dd, 1H, J = 15.6, 5.9 Hz), 7.21 (m, 1H), 7.24–7.35 (m, 10H). HRMS calcd for $C_{34}H_{45}N_5O_7$+Cs 768.2373, found 768.2395.

Example 22 - Preparation of Compound 24: Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Preparation of intermediate Ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-Propenoate.

A solution of HCl in 1,4-dioxane (4.5 mL of a 4.0 M solution) was added to a solution of ethyl-3-[BOC-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.39 g, 0.61 mmol) in the same solvent (4.5 mL) at room temperature. The reaction mixture was stirred for 2 h at rt and then concentrated. The resulting foamy solid was dissolved in dry CH_2Cl_2, and BOC-L-Leu (0.14 g, 0.61 mmol), 1-hydroxybenzotriazole hydrate (0.12 g, 0.92 mmol), 4-methylmorpholine (0.27 mL, 2.45 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.18 g, 0.92 mmol) were added sequentially. The reaction mixture was stirred for 12 h at 23 °C, and then it was partitioned between 1N HCl and CH_2Cl_2. The organic layer was washed with aq sat solution of $NaHCO_3$, dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel (2 % MeOH/$CHCl_3$) to provide ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 68%) as a foamy white

solid. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 6.5 Hz), 0.92 (d, 3H, J = 6.5 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.43 (s, 9H), 1.63-1.72 (m, 3H), 1.97-2.09 (m, 6H), 3.52 (m, 1H), 3.75 (m, 1H), 4.14-4.21 (m, 2H), 4.27 (m, 1H), 4.42-4.52 (m, 2H), 4.86 (m, 1H), 5.85 (dd, 1H, J = 15.6, 1.6 Hz), 6.75-6.82 (m, 2H), 7.07 (s, 1H), 7.19-7.32 (m, 15H). MS calcd for $C_{44}H_{56}N_4O_7$+Cs 885, found 885.

Preparation of Intermediate Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)] -E-Propenoate.

A solution of anh HCl in 1,4-dioxane (3.0 mL of a 4.0 M solution) was added to a solution of ethyl-3-[BOC-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 0.42 mmol) in 3 mL 1,4-dioxane at 23°C. The reaction mixture was stirred for 2 h at 23°C, and it was then concentrated. The resulting foamy white solid was dissolved in dry CH_2Cl_2 and diisopropylethylamine (0.16 mL, 0.91 mmol), and ethylchlorothiolformate (0.052 mL, 0.91 mmol) were added sequentially. The reaction mixture was poured into H_2O, extracted with CH_2Cl_2 twice, and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography on silica gel (2% MeOH/$CHCl_3$) to provide ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 78%) as a glassy white foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.7 Hz), 0.91 (d, 3H, J = 6.7 Hz), 1.27 (t, 6H, J = 7.4 Hz), 1.34 (m, 1H), 1.70-1.72 (m, 2H), 1.96-2.10 (m, 6H), 2.37-2.42 (m, 2H), 2.88 (dd, 2H, J = 14.6, 7.5 Hz), 3.54 (m, 1H), 3.72 (m, 1H), 4.18 (dd, 2H, J = 14.3, 7.2 Hz), 4.25 (m, 1H), 4.52 (m, 1H), 4.75 (m, 1H), 5.78 (m, 1H), 5.85 (dd, 1H, J = 15.8, 1.8 Hz), 6.79 (dd, 1H, J = 15.8, 5.2 Hz), 6.88 (d, 1H, J = 8.1 Hz), 7.11 (s, 1H), 7.20-7.33 (m, 15H). MS calcd $C_{42}H_{52}N_4O_6S$+Cs 873, found 873.

Preparation of Product -Ethyl-3-(Ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-Propenoate.

Trifluoroacetic acid (2.0 mL) was added to a solution of ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate (0.24 g, 0.32 mmol) in chloroform (2.0 mL) and stirred at 23°C for 1 h. The yellow solution evaporated to dryness, and the residue was purified by column chromatography on silica gel (5% MeOH/CHl_3) to provide ethyl-3-(ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-propenoate (0.096 g, 60%) as a glassy white foamy solid. IR (thin film) 3292, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, J = 6.5),

0.98 (d, 3H, J = 6.7 Hz), 1.29 (t, 6H, J = 7.4 Hz), 1.46-1.51 (m, 2H), 1.69-1.79 (m, 3H), 2.00-2.34 (m, 6H), 2.86-2.94 (m, 2H), 3.62 (m, 1H), 3.80 (m, 1H), 4.20 (dd, 2H, J = 14.3, 7.2 Hz), 4.42 (m, 1H), 4.65 (m, 1H), 4.80 (m, 1H), 5.57 (m, 1H), 5.93 (dd, 1H, J = 15.8, 1.5 Hz), 6.41 (m, 1H), 6.49 (m, 1H), 6.86 (dd, 1H, J = 15.8, 5.2 Hz), 7.06 (d, 1H, J = 8.7 Hz). HRMS calcd for $C_{23}H_{38}N_4O_6S$+Cs 499.2590, found 499.2596; Anal ($C_{23}H_{38}N_4O_6S$) C, H, N.

Example 23 - Preparation of Compound 25: Ethyl-3-[CBZ-L-Leu-L-Pip-L-*Gln*]-E-Propenoate.

Preparation of Intermediate CBZ-L-Leu-L-Pip-OtBu.

A suspension of CBZ-L-Pip-OtBu (0.52 g, 1.6 mmol) and Pd on C (10%, 0.10 g) in EtOAc was stirred under a hydrogen atmosphere (balloon) for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The resulting oil was coupled with CBZ-L-Leu (0.43 g, 1.6 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide CBZ-L-Leu-L-Pip-OtBu (0.57 g, 83%) as a colorless oil after column chromatography on silica (20% EtOAc/hexanes): IR (thin film) 3300, 1726, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 6.5 Hz), 1.03 (d, 3H, J = 6.5 Hz), 1.46 (s, 9H), 1.50-1.60 (m, 2H), 1.64-1.83 (m, 2H), 2.23-2.27 (m, 2H), 3.19-3.28 (m, 2H), 3.77-3.81 (m, 2H), 4.76-4.83 (m, 2H), 5.10 (s, 2H), 5.26 (d, 1H, J = 4.7 Hz), 5.60 (d, 1H, J = 8.7 Hz), 7.27-7.36 (m, 5H); Anal. ($C_{24}H_{36}N_2O_5$) C, H, N.

Preparation of Intermediate CBZ-L-Leu-L-Pip.

Trifluoroacetic acid (3 mL) was added to a solution of CBZ-L-Leu-L-Pip-OtBu (0.57 g, 1.3 mmol) in CH_2Cl_2 (6 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 1.5 h after which CCl_4 (6 mL) was added. The volatiles were then removed under reduced pressure to afford crude CBZ-L-Leu-L-Pip as a colorless oil. The crude acid thus obtained was immediately utilized in the following coupling procedure.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.36 g, 0.67 mmol) was deprotected and coupled with CBZ-L-Leu-L-Pip (0.26 g, 0.67 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-

[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenoate (0.20 g, 37%) as a foamy white solid: IR (thin film) 3304, 2954, 1713, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.86 (d, J = 6.5 Hz), 0.94–0.99 (m), 1.22–1.30 (m), 1.32–1.40(m), 1.43–1.50 (m), 1.62–1.68 (m), 1.79–1.98 (m), 2.26–2.45 (m), 3.25 (bs), 3.63–3.77 (m), 4.09–4.21(m), 4.50–4.58 (m), 4.73–4.78 (m), 4.88–5.10 (m), 5.27 (d, J = 7.2 Hz), 5.49 (d, J = 8.7 Hz), 5.82 (dd, J = 15.6, 1.3 Hz), 5.90 (d, J = 15.6 Hz), 6.75 (d, J = 5.3 Hz), 6.79–6.88(m), 7.02–7.36(m); Anal. ($C_{48}H_{56}N_4O_7$) C, H, N.

Preparation of Product-Ethyl-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenoate (0.16 g, 0.18 mmol) was deprotected using the procedure described in Example 1 for the synthesis of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-propenoate (0.082 g, 83%) as a foamy white solid: IR (thin film) 3306, 1713, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.90–1.00(m), 1.23–1.30 (m), 1.41–2.08 (m), 2.12–2.22 (m), 2.44–2.59 (m), 3.41–3.48 (m), 3.80–3.84 (m), 4.12–4.22 (m), 4.54–4.60 (m), 4.79 (bs), 4.99–5.12 (m), 5.79–5.98 (m), 6.11(s), 6.27 (s), 6.79–6.92 (m), 7.14 (d, J = 7.2 Hz), 7.28–7.34 (m), 7.75 (d, J = 7.8 Hz). Anal. ($C_{29}H_{42}N_4O_7 \cdot 0.5\ H_2O$) C, H, N.

Example 24 - Preparation of Compound 26: 1-[1',2'-Oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenone.

Preparation of Intermediate 1,2-Isooxazinane-2-Carboxylic Acid Ethyl Ester.

1,4 Dibromobutane (2.84 mL, 24.0 mmol), N-hydroxyurethane (5.0 g, 48.0 mmol), and KOH (2.67 g, 48.0 mmol) were taken up in 27 mL of EtOH and refluxed for 6 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (50% EtOAc/hexanes) to provide 1,2-isooxazinane-2-carboxylic acid ethyl ester (2.38 g, 68%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz), 1.69–1.81 (m, 4H), 3.69 (t, 2H, J = 5.5 Hz), 3.98 (t, 2H, J = 5.3 Hz), 4.20–4.27 (m, 2H).

Preparation of Intermediate 1,2-Isooxazinane•HCl salt

1,2-Isooxazinane-2-carboxylic acid ethyl ester (2.38 g, 15.0 mmol) was refluxed in concentrated HCl for 3 h. The reaction mixture was cooled to rt and washed with Et_2O. The

organic phase was discarded, and the aqueous layer was concentrated in vacuo. Traces of H_2O were removed by adding EtOH and reconcentrating. This yielded the HC1 salt of 1,2-isooxazinane as a white solid (1.70 g, 92%) which was dried before subsequent use. ^{1}H NMR (CD_3OD) δ 1.86-1.90 (m, 2H), 1.96-2.02 (m, 2H), 3.52-3.46 (m, 2H), 4.25-4.29 (m, 2H), 4.88 (bs, 1H). MS calcd for $C_4H_{10}NO$ 87, found 87.

Preparation of Intermediate 1-[1', 2'-Oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-Propenone

1,2-Isooxazinane-HCl (0.12 g, 0.97 mmol) was coupled with 3-[BOC-L-(Tr-*Gln*)]-E-propenoic acid (0.50 g, 0.97 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide 1-[1', 2'-oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-propenone (0.43 g, 76%) as a glassy white solid. ^{1}H NMR ($CDC1_3$) δ 1.43 (s, 9H), 1.71-1.83 (m, 5H), 1.94 (m, 1H), 2.35-2.39 (m, 2H), 3.80-3.85 (m, 2H), 3.93-3.96 (m, 2H), 4.33 (m, 1H), 4.76 (m, 1H), 6.54 (d, 1H, J = 15.3 Hz), 6.79 (dd, 1H, J = 15.6, 5.6 Hz), 6.96 (m, 1H), 7.20-7.32 (m, 15H); MS calcd for $C_{35}H_{41}N_3O_5$+H 584, found 584.

Preparation of Intermediate 1-[1', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-Propenone.

1-[1', 2'-oxazin-2'-yl]-3-(BOC-L-*Gln*)-E-propenone (0.36 g, 0.66 mmol) was deprotected and coupled with CBZ-L-Leu-L-Pip (0.26 g, 0.66 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide 1-[1', 2'-oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenone (0.14 g, 26%) as a foamy white solid: IR (thin film) 3301, 1658, 1630 cm^{-1}; ^{1}H NMR ($CDC1_3$, mixture of rotamers) δ 0.86 (d, J = 6.9 Hz), 0.94-0.99 (m), 1.28-1.40 (m), 1.52-1.57 (m), 1.64-2.01(m), 2.27-2.55 (m), 3.27 (s, bs), 3.73-3.94 (m), 4.46-4.64 (m), 4.73-4.92 (m), 5.05 (s), 5.10 (s), 5.30 (s), 5.52 (d, J = 9.0 Hz), 6.48-6.61(m), 6.74-6.79 (m), 6.81-6.95 (m), 7.17-7.37 (m), 7.72 (d, J = 8.4 Hz).

Preparation of Product-1-[1', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-*Gln*)-E-Propenone.

1-[1', 2'-Oxazin-2'-yl]-3-[CBZ-L-Leu-L-Pip-L-(Tr-*Gln*)]-E-propenone (0.14 g, 0.17 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide 1-[1', 2'-oxazin-2'-yl]-3-(CBZ-L-Leu-L-Pip-L-*Gln*)-E-propenone (0.060 g, 59%) as a foamy white solid: IR (thin film) 3305, 1660,

1630 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.91 (d, J = 6.9 Hz), 0.94–0.97(m), 0.92 (d, J = 6.5 Hz), 1.26–1.82(m), 1.93–2.29(m), 2.45 (d, J = 12.1 Hz), 2.56–2.65 (m), 3.47 (s), 3.73–3.96 (m), 4.49–4.83 (m), 4.99 (s), 5.04 (s), 5.09 (s), 5.13 (s), 5.60–5.66(m), 5.72–5.85(m), 6.18(s), 6.31(s), 6.54–6.63 (m), 6.79–6.91(m), 7.14 (d, J = 7.8 Hz), 7.28–7.34 (m), 7.71 (d, J = 8.1 Hz). Anal. ($C_{31}H_{45}N_5O_7$) C, H, N.

Example 25 - Preparation of Compound 27: Ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-Propenoate.

Preparation of Intermediate FMOC-L-Leu-DL-(4-BOC)-Pipz.

To a suspension of DL-(4-BOC)-piperazine-3-carboxylic acid (0.20 g, 0.87 mmol) in dry CH_2Cl_2 (10 mL) was added 4-methylmorpholine (0.21 mL, 1.91 mmol) and trimethylsilylchloride (0.13 g, 1.04 mmol) at rt. A clear, homogeneous solution formed after ~2 h. To this solution was added the FMOC-L-Leu-Cl (0.32 g, 0.87 mmol) (Advanced ChemTech), and the mixture was stirred at rt overnight. At this time, the reaction mixture was poured into H_2O and extracted twice with CH_2Cl_2, dried over $MgSO_4$ and concentrated to provide FMOC-L-Leu-DL-(4-BOC)-Pipz (0.45 g, 91%) as a pale yellow foamy solid. ^1H NMR ($CDCl_3$) δ 0.87–1.04 (m, 6H), 1.44 (s, 9H), 1.51 (m, 1H), 1.74 (m, 1H), 2.89–3.10 (m, 2H), 3.67 (m, 1H), 4.03 (m, 1H), 4.21–4.42 (m, 7H), 4.56–4.77 (m, 3H), 7.25–7.77 (m, 8H). MS calcd for $C_{31}H_{39}N_3O_7$+Cs, 698, found 698.

Preparation of Intermediate Ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)] -E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.59 g, 1.23 mmol) was deprotected and coupled to FMOC-L-Leu-DL-(4-BOC)-Pipz (0.70 g, 1.23 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.60 g, 49 %) as a white foamy solid. ^1H NMR ($CDCl_3$) δ 0.87–1.03 (m, 6H), 1.18–1.30 (m, 3H), 1.44 (s, 9H), 2.00 (m, 1H), 2.24 (m ,1H), 2.38 (m, 1H), 3.06–3.13 (m, 2H), 3.69–3.77 (m, 2H), 3.89 (m, 1H), 4.07–4.24 (m, 6H), 4.33–4.59 (m, 9H), 5.85 (m, 1H), 6.75–6.88 (m, 2H), 7.19–7.78 (m, 23H). MS calcd for $C_{59}H_{67}N_5O_9$+Cs 1122, found 1122.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)] E-Propenoate.

To a solution of ethyl-3-[FMOC-L-Leu-DL-(4-BOC)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.60 g, 0.60 mmol) in $CHCl_3$ was added 4-(aminomethyl)piperidine (5 mL) at rt. The reaction mixture was stirred for 1 h and then sequentially washed twice with sat brine, 5 times with 10% aq K_2HPO_4 buffer (pH 5.5), and once with a sat solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated. The resulting oil (0.34 g, 0.44 mmol) was dissolved in dry CH_2Cl_2 (30 mL). 4-Methylmorpholine (0.24 g, 2.20 mmol) was added followed by benzylchloroformate (0.13 g, 0.88 mmol), and the mixture was stirred for 4 h at rt. This mixture was then poured into H_2O and extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (5% MeOH/$CHCl_3$) providing ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.31 g, 77 %) as a white solid foam. ^{1}H NMR ($CDCl_3$) δ 0.82-1.00 (m, 6H), 1.23-1.28 (m, 3H), 1.40-1.58 (m, 2H), 1.67 (m, 1H), 1.98 (m, 1H), 2.26 (m, 1H), 2.37 (m, 1H), 2.75 (m, 1H), 3.07-3.11 (m, 2H), 3.50-4.06 (m, 4H), 4.13 - 4.20 (m, 2H), 4.52-5.15 (m, 6H), 5.87 (m, 1H), 6.75-7.03 (m, 2H), 7.08-7.41 (m, 20H). MS calcd for $C_{52}H_{63}N_5O_9$+Cs 1034, found 1034.

Preparation of Product Ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-Propenoate.

The BOC and trityl protecting groups were both removed from ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.10 g, 0.11 mmol) with trifluoroacetic acid as described in Example 4 for the preparation of ethyl-3-(cyclopentylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenoate to provide ethyl-3-(CBZ-L-Leu-DL-Pipz-L-*Gln*)-E-propenoate (24.0 mg, 39 %) as a solid white foam. IR (thin film) 3308, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91-1.01 (m, 6H), 1.24-1.30 (m, 3H), 1.49 (m, 1H), 1.59 (m, 1H), 1.65-1.86 (m, 3H), 1.98 (m, 1H), 2.15-2.24 (m, 2H), 2.67-2.75 (m, 2H), 3.06 (m, 1H), 3.30 (m, 1H), 3.72-3.82 (m, 2H), 4.14-4.21 (m, 2H), 4.57-4.64 (m, 2H), 5.01-5.13 (m, 3H), 5.58 (m, 1H), 5.76 (d, 1H, J = 6.5 Hz), 5.90-5.98 (m, 2H), 6.88 (dd, 1H, J = 15.6, 5.6 Hz), 7.33 (s, 10H), 7.60 (d, 1H, J = 7.2 Hz). HRMS calcd for $C_{28}H_{41}N_5O_7$+Cs 692.2062, found 692.2040.

Example 26 - Preparation of Compound 28: Ethyl-3-(CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-(Tr-*Gln*)]-E-Propenoate.

A solution of anh HC1 in 1,4-dioxane (3.0 mL of a 4.0 M solution) was added to a solution of ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.18 g, 0.20 mmol) in 1,4-dioxane (3.0 mL) at rt. The reaction mixture was stirred for 2 h at rt, and then concentrated under vacuum. The resulting foamy residue was taken up in EtOAc, washed with a sat $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The resulting yellow oil was dissolved in 3.0 mL of DMF. To this solution was added NaH (5.0 mg, 0.20 mmol), followed by benzyl bromide (0.024 mL, 0.20 mmol) after a few minutes. The reaction mixture was stirred at rt overnight. The mixture was then concentrated under vacuum and 10 mL H_2O was added to the residue. CH_2C1_2 was used to extract the aq. phase twice, which was dried over $MgSO_4$, concentrated, and purified using prep TLC (5% MeOH/$CHC1_3$), providing ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.10 g, 56 %) as a yellow foamy solid. ^1H NMR ($CDC1_3$) δ 0.82–0.94 (m, 6H), 1.21–1.32 (m, 4H), 1.48–1.66 (m, 3H), 1.97–2.13 (m, 2H), 2.25–2.35 (m, 2H), 2.81 (m, 1H), 3.38–3.52 (m, 3H), 3.64–3.76 (m, 3H), 4.14–4.24 (m, 2H), 4.46–5.22 (m, 6H), 5.96 (m, 1H), 6.75–7.04 (m, 2H), 7.15–7.35 (m, 25H), 7.51 (m, 1H). MS calcd for $C_{54}H_{61}N_5O_7$+H 892, found 892.

Preparation of Product-Ethyl-3-[CBZ-L-Leu-DL-(4-Benzyl)-Pipz-L-*Gln*]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.090 g, 0.10 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-DL-(4-benzyl)-Pipz-L-*Gln*]-E-propenoate (0.030 g, 45 %) as a solid white foam. IR (thin film) 3323, 1708 cm^{-1}; ^1H NMR ($CDC1_3$) δ 0.94–0.99 (m, 6H), 1.27–1.32 (m, 3H), 1.48 (m, 1H), 1.56 (m, 1H), 1.71–2.17 (m, 6H), 2.83 (m, 1H), 3.37-3.50 (m, 2H), 3.68–3.72 (m, 2H), 4.19–4.24 (m, 3H), 4.60–4.70 (m, 2H), 5.00–5.28 (m, 2H), 5.61–5.92 (m, 4H), 6.03 (m, d, 1H, J = 15.6 Hz), 6.87–6.92 (m, 2H), 7.26–7.32 (m, 10H), 7.78 (m, 1H). HRMS calcd for $C_{35}H_{47}N_5O_7$+Cs 782.2530, found 782.2546.

Example 27 - Preparation of Compound 29: Ethyl-3-[CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-*Gln*]-E-Propenoate.

Preparation of Intermediate Ethyl-3-[CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-Propenoate.

A solution of anh HCl in 1,4-dioxane (2.5 mL of a 4.0 M solution) was added to a solution of ethyl-3-[CBZ-L-Leu-(4-BOC)-DL-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.16 g, 0.18 mmol) in 1,4-dioxane (2.5 mL) at room temperature. The reaction mixture was stirred for 2 h at rt, and then it was concentrated under vacuum. The resulting foam was dissolved in dry CH_2Cl_2, and phenylsulfonyl chloride (0.046 mL, 0.36 mmol) and 4-methylmorpholine (0.10 mL, 0.91 mmol) were added at rt and stirred for 2 h. The reaction mixture was poured into H_2O and extracted twice with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give a residue that was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to provide ethyl-3-[CBZ-L-Leu-DL-(4-phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.057 g, 33%) as an off-white foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.86-0.93 (m, 6H), 1.25-1.32 (m, 3H), 1.48 (m, 1H), 1.63 (m, 1H), 2.25-2.36 (m, 4H), 3.52 (m, 1H), 3.71-3.78 (m, 4H), 4.12-4.25 (m, 4H), 4.45 (m, 1H), 4.64 (m, 1H), 4.92-5.39 (m, 5H), 5.94 (m, 1H), 6.34 (m, 1H), 7.18-7.31 (m, 20H), 7.48-7.67 (m, 5H), 7.77 (m, 1H). MS calcd for $C_{53}H_{59}N_5O_9S$+Cs 1074, found 1074.

Preparation of Product Ethyl-3-(CBZ-L-Leu-DL-(4-Phenylsulfonyl)-Pipz-L-*Gln*)]-E-Propenoate.

Ethyl-3-[CBZ-L-Leu-DL-(4-phenylsulfonyl)-Pipz-L-(Tr-*Gln*)]-E-propenoate (0.057 g, 0.06 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate, to provide ethyl-3-[CBZ-L-Leu-DL- (4-phenylsulfonyl)-Pipz-L-*Gln*)]-E-propenoate (22.0 mg, 52%) as a white foamy solid. IR (thin film) 3322, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) 5 0.89-0.98 (m, 6H), 1.22-1.33 (m, 3H), 1.52 (m, 1H), 2.19-2.51 (m, 4H), 3.68-3.78 (m. 5H), 4.14-4.25 (m, 4H), 4.59-4.63 (m, 2H), 5.03-5.11 (m, 3H), 5.21 (m, 1H), 5.43 (m, 1H), 5.57 (m, 1H), 5.94 (m, 1H), 6.85 (m, 1H), 7.20-7.34 (m, 5H), 7.55-7.62 (m, 3H), 7.74-7.80 (m, 2H). HRMS calcd for $C_{34}H_{45}N_5O_9S$+Cs 832.1992, found 832.1982.

Example 28 - Preparation of Compound 32:
Ethyl-3-(L-N-[(1,3-Dihydro-imidazol-2-one)- *Phe*]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate
Ethyl-3-[L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-Propenoate.

A solution of Phe-OtBu•HCl (0.77 g, 2.99 mmol) and triethylamine (0.833 mL, 5.98 mmol) in CH_2Cl_2 (10 mL) was added via cannula to a solution of triphosgene (0.295 g, 0.994 mmol) in CH_2Cl_2 (25 mL) at 23 °C. The reaction mixture was stirred at that temperature for 5 min, and then it was heated to reflux for 1 h. After cooling to 23 °C, a solution of aminoacetaldehyde dimethyl acetal (0.314 g, 2.99 mmol) and triethylamine (0.417 mL, 2.99 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The reaction mixture was stirred for 3 h at 23 °C and then partitioned between half-saturated NH_4Cl (100 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided the intermediate urea as a colorless oil (0.36 g, 34%).

This material was dissolved in CH_2Cl_2 (20 mL) at 23 °C. Trifluoroacetic acid (10 mL) was added, and the reaction mixture was stirred at 23 °C for 1 h and then concentrated under reduced pressure. The resulting oil was partitioned between 10% NaOH (100 mL) and Et_2O (2 x 100 mL). The aqueous layer was acidified with concentrated HCl to pH = 2 (as indicated by pH paper) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude L-N-(1,3-dihydro-imidazol-2-one)-Phe (0.125 g, 53%) as a white solid. This material was dissolved in DMF (10 mL) and crude ethyl-3-[L-(Tr-*Gln*)]-E-propenoate•HCl (0.603 mmol) (generated as described in the first deprotection step in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), 1-hydroxybenzotriazole hydrate (0.122 g, 0.903 mmol), 4-methylmorpholine (0.2 mL, 1.81 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.173 g, 0.903 mmol) were added sequentially, and the reaction mixture was stirred for 18 h at 23 °C and then concentrated under reduced pressure. The resulting oil was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided

ethyl-3-[L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.129 g, 33%) as a solid yellow foam: R_f = 0.42 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3265, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.2), 1.68-1.78 (m, 1H), 1.89-1.95 (m, 1H), 2.27-2.33 (m, 2H), 3.06 (dd, 1H, *J* = 13.6, 7.3), 3.27 (dd, 1H, *J* = 13.6, 8.4), 4.18 (q, 2H, *J* = 7.2), 4.38 (bs, 1H), 4.96-5.02 (m, 1H), 5.62 (dd, 1H, *J* = 15.7, 1.6), 5.87-5.89 (m, 1H), 6.51-6.53 (m, 1H), 6.62 (dd, 1H, *J* = 15.7, 5.6), 6.90 (s, 1H), 7.00-7.33 (m, 20H), 7.79 (d, 1H, *J* = 7.5), 8.06 (s, 1H).

Preparation of Product - Ethyl-3-(L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Ethyl-3-[L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate(0.129g,0.196 mmol) was deprotected according to the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate.

Ethyl-3-(L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-propenoate (0.037 g, 46%) was isolated as a solid beige foam after removal of organic solvents and trituration with 4:1 Et_2O:CH_3CN, followed by filtration and washing with 2 x 10 mL Et_2O and air drying. R_f= 0.15 (10% CH_3OH/CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, *J* = 7.2), 1.61-1.80 (m, 2H), 2.01-2.07 (m, 2H), 3.01-3.17 (m, 2H), 4.11 (q, 2H, *J* = 7.2), 4.32-4.41 (m, 1H), 4.87-4.92 (m, 1H), 5.68 (dd, 1H, *J* = 15.7, 1.4), 6.24-6.26 (m, 1H), 6.63-6.72 (m, 2H), 6.74 (s, 1H), 7.12-7.25 (m, 6H), 8.44 (d, 1H, *J* = 8.1), 9.83 (s, 1H); Anal. ($C_{21}H_{26}N_4O_5$•0.5 H_2O) C, H, N.

Example 29 - Preparation of Compound 33: Ethyl-3-(CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate 1-CBZ-2-(2,2-Dimethoxyethyl)-Hydrazine.

Aminoacetaldehyde dimethyl acetal (0.430 g, 3.95 mmol) was added to a solution of N-CBZ-3-phenyl-oxaziridine (1.11 g, 4.35 mmol) (prepared as described in *Tetrahedron Lett.* **1993**, 6859, the disclosure of which is entirely incorporated herein by reference) in CH_2Cl_2 (20 mL) at 23°C. The resulting yellow solution was stirred at 23°C for 18 h, and it then was concentrated under reduced pressure. Purification of the residue by flash column chromatography (3% CH_3OH/CH_2Cl_2) provided 1-CBZ-2-(2,2-dimethoxyethyl)-hydrazine (0.434 g, 43%) as a pale yellow oil: R_f= 0.40 (5% CH_3OH/CH_2Cl_2); IR (thin film) 3317, 1721,

1456 cm^{-1}; ^1H NMR (C_6D_6) δ 2.96 (bs, 2H), 3.06 (bs, 6H), 3.97 (bs, 1H), 4.37 (bs, 1H), 4.97 (bs, 2H), 5.87 (bs, 1H), 6.98-7.18 (m, 5H).

Preparation of Intermediate Ethyl-3-[CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-Propenoate.

A solution of Phe-OtBu•HCl (0.440 g, 1.71 mmol) and triethylamine (0.345 mL, 2.47 mmol) in CH_2Cl_2 (20 mL) was added via cannula to a solution of triphosgene (0.168 g, 0.566 mmol) in CH_2Cl_2 (40 mL) at 23 °C. The reaction mixture was stirred at that temperature for 5 min, and then it was heated to reflux for 1 h. After cooling to 23 °C, a solution of 1-CBZ-2-(2,2-dimethoxyethyl)-hydrazine (0.434 g, 1.71 mmol) and triethylamine (0.173 mL, 1.24 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The reaction mixture was stirred for 1 h at 23 °C, and then it was partitioned between half-saturated NH_4Cl (100 mL) and EtOAc (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (3% CH_3OH/CH_2Cl_2) provided the intermediate urea as a colorless oil (0.56 g, 65%). This material was dissolved in CH_2Cl_2 (20 mL) at 23 °C. Trifluoroacetic acid (10 mL) was added, and the reaction mixture was stirred at 23 °C for 1.5 h. CCl_4 (10 mL) was added, and the mixture was concentrated under reduced pressure. The resulting oil was partitioned between 10% NaOH (100 mL) and Et_2O (2 x 100 mL). The aqueous layer was acidified with concentrated HCl to pH = 2 (as indicated by pH paper) and was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude CBZ-amino-L-N-(1,3-dihydro-imidazol-2-one)-*Phe* (0.374 g, 89%) as a solid white foam. This material was dissolved in CH_2Cl_2 (10 mL) and crude ethyl-3-[L-(Tr-*Gln*)]-E-propenoate•HCl (0.981 mmol) (generated as described in the first deprotection step in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), 1-hydroxybenzotriazole hydrate (0.172 g, 1.27 mmol), 4-methylmorpholine (0.323 mL, 2.94 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.244 g, 1.27 mmol) were added sequentially. The reaction mixture was stirred for 18 h at 23 °C, and it then was partitioned between water (100 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (5% CH_3OH/CH_2Cl_2) provided ethyl-3-[CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.449 g, 57%) as a solid white foam:

R_f = 0.44 (10% CH_3OH in CH_2Cl_2); IR (thin film) 3284, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 1H, J = 7.2), 1.42–1.44 (m, 1H), 2.00–2.16 (m, 3H), 3.08 (dd, 1H, J = 13.4, 7.5), 3.32–3.39 (m, 1H), 4.01–4.18 (m, 3H), 4.47 (bs, 1H), 4.90 (bs, 2H), 4.99–5.04 (m, 1H), 5.60 (dd, 1H, J = 16.0, 1.6), 5.86 (bs, 1H), 6.54 (d, 1H, J = 3.1), 6.66 (dd, 1H, J = 16.0, 4.5), 6.94–7.32 (m, 26H), 7.83 (s, 1H); Anal. ($C_{48}H_{47}N_5O_7$•0.5 H_2O) C, H, N.

Preparation of Product Ethyl-3-(CBZ-amino-L-N-[(1,3-Dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-Propenoate.

Ethyl-3-[CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-(Tr-*Gln*)]-E-propenoate (0.147 g, 0.182 mmol) was deprotected according to the procedure described in Example 1 for the preparation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate. Ethyl-3-(CBZ-amino-L-N-[(1,3-dihydro-imidazol-2-one)-*Phe*]-L-*Gln*)-E-propenoate (0.042 g, 40%) was isolated as a white solid after removal of organic solvents and trituration with Et_2O, followed by filtration and washing with 2 x 10 mL Et_2O and air drying: mp = 216–218°C; R_f = 0.27 (10% CH_3OH/CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, J = 7.2), 1.61–2.06 (m, 2H), 2.01–2.06 (m, 2H), 3.11–3.13 (m, 2H), 3.36–3.38 (m, 1H), 4.11 (q, 2H, J = 7.2), 4.34–4.38 (m, 1H), 4.90–4.96 (m, 1H), 5.09 (bs, 2H), 5.66 (d, 1H, J = 15.7), 6.53 (d, 1H, J = 2.8), 6.69 (dd, 1H, J = 15.7, 5.6), 6.75–6.77 (m, 2H), 7.21 (bs, 6H), 7.37 (bs, 4H), 8.52 (d, 1H, J = 8.1), 10.14 (s, 1H); Anal. ($C_{29}H_{33}N_5O_7$) C, H, N.

Example 30 - Preparation of Compound 34:
Ethyl-3-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

This material was prepared from ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.832 g, 1.53 mmol) and BOC-L-Val-L-N-Me-Phe (0.570 g, 1.51 mmol) using the method described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (gradient: 43%–50% EtOAc in hexanes) as a white foam (0.789 g, 64%): IR (thin film) 3295, 1708, 1660 cm-^{1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.66–0.73 (m), 0.81 (d, J = 6.8 Hz), 0.86 (d, J = 6.8 Hz), 1.23–1.37 (m), 1.35 (s), 1.42 (s), 1.62–1.85 (m), 1.88–2.06 (m), 2.20–2.27 (m), 2.83–3.03 (m), 2.88 (s), 2.99 (s), 3.31 (dd, J =

14.0, 8.2 Hz), 3.41 (dd, J = 14.0, 5.8 Hz), 4.03–4.10 (m), 4.16 (q, J = 7.2 Hz), 4.17 (q, J = 7.2 Hz), 4.27–4.34 (m), 4.45–4.56 (m), 4.57–4.70 (m), 4.88–5.03 (m), 5.59 (d, J = 15.7 Hz), 5.87 (d, J = 15.7 Hz), 6.20 (d, J = 8.4 Hz), 6.66 (dd, J = 15.7, 5.1 Hz), 6.80 (dd, J = 15.7, 6.1 Hz), 6.89–7.05 (m), 7.12–7.34 (m), 7.88 (d, J = 8.1 Hz). Anal. ($C_{48}H_{58}N_4O_7$•0.5 H_2O) C, H, N.

Preparation of Intermediate Ethyl-3-[Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.366 g, 0.456 mmol) was deprotected and coupled with ethyl chlorothiolformate (0.057 mL, 0.55 mmol) as described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (gradient: 44%-50% EtOAc in hexanes) as a white foam (0.217 g, 60%): IR (thin film) 3295, 1713, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.48 (d, J = 6.5 Hz), 0.71 (d, J = 6.8 Hz), 0.80–0.89 (m), 1.17–1.22 (m), 1.58–2.06 (m), 2.19–2.32 (m), 2.65–3.04 (m), 2.84 (s), 2.97 (s), 3.29–3.43 (m), 4.18 (q, J = 7.2 Hz), 4.49–4.59 (m), 4.65–4.71 (m), 4.75–4.83 (m), 5.65 (dd, J = 15.9, 1.6 Hz), 5.71–5.76 (m), 5.81–5.90 (m), 6.31–6.36 (m), 6.70 (dd, J = 15.9, 5.3 Hz), 6.79 (dd, J = 15.9, 5.9 Hz), 6.88 (s), 7.01(s), 7.12–7.34 (m), 7.75–7.80 (m). Anal. ($C_{46}H_{54}N_4O_6S$•0.5 H_2O) C, H, N.

Preparation of Product -
Ethyl-3-(Ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.187 g, 0.236 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-(CBZ-L-N-Me-Phe-L-*Gln*)-E-propenoate to give ethyl-3-(ethylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-propenoate after column chromatography (50% acetone in hexanes, then 6% MeOH in CH_2Cl_2) as a white foam (0.076 g, 58%): IR (thin film) 3307, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.47 (d, J = 6.5 Hz), 0.77 (d, J = 6.8 Hz), 0.92 (d, J = 6.5 Hz), 0.93 (d, J = 6.5 Hz), 1.25 (t, J = 7.2 Hz), 1.29 (t, J = 7.2 Hz), 1.42–1.54(m), 1.64–1.79(m), 1.80–2.03 (m), 2.08–2.31 (m), 2.73–3.01(m), 2.92 (s), 3.04–3.15 (m), 3.07 (s), 3.31–3.47 (m), 4.16–4.26 (m), 4.19 (q, J = 7.2 Hz), 4.51–4.65 (m), 4.70–4.78 (m), 5.72 (dd, J = 15.6, 1.6 Hz),

5.85–6.05 (m), 6.19 (bs), 6.56 (d, J = 8.1 Hz), 6.75 (dd, J = 15.6, 5.3 Hz), 6.80–6.89 (m), 7.15–7.35(m), 7.46 (d, J = 7.8 Hz). Anal. ($C_{27}H_{40}N_4O_6S$) C, H, N.

Example 31 - Preparation of Compound 35: Ethyl-3-(Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-[Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.365 g, 0.455 mmol) was deprotected and coupled with cyclopentyl chlorothiolformate (0.09 mL, about 0.5 mmol) using the procedure described in Example 6 for the formation of 1-(2',3'-dihydroindolin-1-yl)-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenone to give ethyl-3-[cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate after column chromatography on silica gel (40%–50% EtOAc in hexanes) as a white foam (0.231 g, 61%): IR (thin film) 3295, 1713, 1655, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.50 (d, J = 6.5 Hz), 0.73 (d, J = 6.8 Hz), 0.80–0.88 (m), 1.22–2.31 (m), 2.84–3.04 (m), 2.86 (s), 2.98 (s), 3.29–3.41 (m), 3.54–3.69 (m), 4.08–4.25 (m), 4.17 (q, J = 7.2 Hz), 4.48–4.63 (m), 4.67–4.82 (m), 5.64 (dd, J = 15.7, 1.6 Hz), 5.76–5.82 (m), 5.83–5.91 (m), 5.87 (dd, J = 15.7, 1.6 Hz), 6.39–6.45 (m), 6.70 (dd, J = 15.7, 5.3 Hz), 6.79 (dd, J = 15.7, 5.8 Hz), 6.93 (s), 7.06 (s), 7.12–7.33 (m), 7.72 (d, J = 7.8 Hz). Anal. ($C_{49}H_{58}N_4O_6S \cdot 0.5\ H_2O$) C, H, N.

Preparation of Product-
Ethyl-3-(Cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-Propenoate.

Ethyl-3-[cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate (0.179 g, 0.215 mmol) was deprotected using the procedure described in Example 1 for the formation of ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate to give ethyl-3-(cyclopentylthiocarbonyl-L-Val-L-N-Me-Phe-L-*Gln*)-E-propenoate after column chromatography on silica gel (50% acetone in hexanes, then 6% MeOH in CH_2Cl_2) as a white foam (0.086 g, 68%): IR (thin film) 3295, 1713, 1666, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.48 (d, J = 6.5 Hz), 0.77 (d, J = 6.8 Hz), 0.92 (d, J = 6.5 Hz), 0.93 (d, J = 6.8 Hz), 1.29 (t, J = 7.2 Hz), 1.37–1.79 (m), 1.81–2.29 (m), 2.91–3.00 (m), 2.92 (s), 3.03–3.15 (m), 3.06 (s), 3.34 (dd, J = 14.0, 5.3 Hz), 3.43 (dd, J = 14.0, 6.7 Hz), 3.59–3.69 (m), 4.16–4.26 (m), 4.18 (q, J = 7.2 Hz), 4.52–4.65 (m), 4.68–4.77 (m), 5.72 (dd, J = 15.9, 1.6 Hz), 5.78 (bs),

5.85 (bs), 5.90 (dd, J = 15.6, 1.2 Hz), 6.01 (bs), 6.19 (bs), 6.42 (d, J = 8.1 Hz), 6.67 (d, J = 9.0 Hz), 6.75 (dd, J = 15.6, 5.3 Hz), 6.80–6.87 (m), 7.16–7.34 (m), 7.42 (d, J = 7.8 Hz). Anal. ($C_{30}H_{44}N_4O_6S$) C, H, N.

Example 32 - Preparation of Compound 36: N-Methoxy-N-Methyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenamide.

Preparation of Intermediate N-Methoxy-N-Methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-(Tr-*Gln*)]-E-propenamide (0.29 g, 0.58 mmol) was deprotected and coupled to BOC-L-Leu-L-N-Me-Phe (0.23 g, 0.58 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate to provide N-methoxy-N-methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.23 g, 47%) as a white solid foam after column chromatography on silica (2% methanol/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.63–0.66 (m, 6H), 0.71 (m, 1H), 0.86–0.95 (m, 3H), 1.06 (m, 1H), 1.31–1.44 (m, 9H), 1.84 (m, 1H), 2.00 (m, 1H), 2.25–2.28 (m, 2H), 2.91–3.00 (m, 3H), 3.23 (s, 3H), 3.66–3.68 (m, 3H), 4.13 (m, 1H), 4.58 (m, 1H), 4.71 (m, 1H), 4.86 (m, 1H), 6.35 (m, 1H), 6.55 (m, 1H), 6.80 (m, 1H), 7.10–7.33 (m, 20H), 8.20 (d, 1H, J = 8.7 Hz). MS calcd for $C_{49}H_{61}N_5O_7$+Na 854, found 854.

Preparation of Intermediate N-Methoxy-N-Methyl 3-[Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-Propenamide.

N-Methoxy-N-methyl-3-[BOC-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide(0.098 g, 0.13 mmol) was deprotected and treated with ethylchlorothiolformate (0.016 mL, 0.15 mmol) using the procedure described in Example 22 for the preparation of ethyl-3-[ethylthiocarbonyl-L-Leu-L-Pro-L-(Tr-*Gln*)]-E-propenoate, to provide N-methoxy-N-methyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.041 g, 39 %) as a clear glass. ^{1}H NMR ($CDCl_3$) δ 0.61–0.75 (m, 3H), 0.80–0.88 (m, 2H), 1.15–1.27 (m, 4H), 1.34–1.44 (m, 2H), 1.65–1.96 (m, 5H), 2.25–2.33 (m, 2H), 2.72–3.05 (m, 3H), 3.20 (s, 3H), 3.66 (s, 3H), 4.61 (m, 1H), 5.77 (dd, 1H, J = 17.4, 7.5 Hz), 6.49 (m, 1H), 6.83 (m, 1H), 7.12 (m, 1H), 7.19–7.33 (m, 20H), 8.01 (d, 1H, J = 8.1 Hz). MS calcd for $C_{47}H_{57}N_5O_6S$+Cs MS calcd for 952, found 952.

PreparationofProductN-Methoxy-N-Methyl-3-(Ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-Propenamide.

N-Methoxy-N-methyl-3-[ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenamide (0.040 g, 0.049 mmol) was deprotected using the procedure described in Example 1 for the preparation ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate, to provide N-methoxy-N-methyl-3-(ethylthiocarbonyl-L-Leu-L-N-Me-Phe-L-*Gln*)-E-propenamide (17.0 mg, 61%) as a white foam after column chromatography (2% methanol/$CHCl_3$). IR (thin film) 3274, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63–0.64 (m, 3H), 0.91 (d, 2H, J = 6.2 Hz), 1.22–1.28 (m, 4H), 1.43 (m, 1H), 1.63 (m, 1H), 1.95–2.02 (m, 2H), 2.80–2.98 (m, 4H), 3.25 (s, 3H), 3.69–3.70 (m, 3H), 4.42 (m, 1H), 4.62–4.66 (m, 2H), 6.09 (m, 1H), 6.18 (dd, 1H, J = 15.0, 7.5 Hz), 6.57 (m, 1H), 6.82 (m, 1H), 7.15–7.34 (m, 7H), 7.89 (d, 1H, J = 8.4 Hz). HRMS calcd for $C_{28}H_{43}N_5O_6S$+Cs 710.1988, found 710.2014.

Example 33 - Preparation of Compound 30: Ethyl-3-([(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*)-E-Propenoate.

Preparation of Intermediate Ethyl-3-{[(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-(Tr-*Gln*)}-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.39 g, 0.72 mmol) was deprotected and coupled with [(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid (0.28 g, 0.73 mmol) (prepared according to the procedure of C.A. Veale, et al., *J. Med. Chem.* **1995**, *38, 98*, the disclosure of which is entirely incorporated herein by reference) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate), to give ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]-L-(Tr-*Gln*)}-E-propenoate (0.43 g, 73%) as a white solid after column chromatography on silica (3% methanol/$CHCl_3$): mp = 106–112°C; IR (thin film) 3297, 1722, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 1.76–1.86 (m, 1H), 1.93–2.04 (m, 1H), 2.36–2.52 (m, 2H), 4.07–4.30 (m, 5H), 4.51 (bs, 1H), 5.21 (s, 2H), 5.81 (dd, 1H, J = 15.6, 1.6 Hz), 6.73 (dd, 1H, J = 15.6, 4.8 Hz), 6.86 (s, 1H), 7.08–7.23 (m, 15 H), 7.29–7.54 (m, 11H), 8.73 (bs, 1H); Anal. ($C_{48}H_{45}N_5O_7$•1.0 H_2O) C, H, N.

Preparation of Product Ethyl-3-{[(5-CBZ-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*}-E-Propenoate.

Ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]-L-(Tr-*Gln*)}-E-propenoate (0.22 g, 0.27 mmol) was deprotected using the procedure described in Example 1 for the preparation of ethyl-3-[CBZ-L-N-Me-Phe-L-*Gln*]-E-propenoate, to provide ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-l-pyrimidinyl]-L-*Gln*}-E-propenoate (0.12 g, 79%) as a white solid after removal of organic solvents and trituration with Et_2O, followed by filtration and washing with 2 x 10 mL Et_2O and air drying: mp = 200–205°C; IR (thin film) 3278, 1719, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 1.56–1.68 (m, 1H), 1.71–1.77 (m, 1H), 2.01–2.06 (m, 2H), 4.13 (q, 2H, J = 7.2 Hz), 4.39–4.55 (m, 3H), 5.18 (s, 2H), 5.78 (dd, 1H, J = 15.9, 1.6 Hz), 6.70–6.77 (m, 2H), 7.24 (s, 1H), 7.30–7.55 (m, 10H), 8.34 (d, 1H, J = 8.1 Hz), 8.45 (s, 1H), 8.94 (s, 1H); Anal. ($C_{29}H_{31}N_5O_7$•0.25 H_2O) C, H, N.

Example 34 - Preparation of Compound 31: Ethyl-3-{[(5-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-*Gln*}-E-Propenoate.

Preparation of Product Ethyl-3-{[(5-Amino)-2-Phenyl-6-Oxo-1,6-Dihydro-1-Pyrimidinyl]-L-Gln}-E-Propenoate.

Borontribromide (0.18 mL of a 1.0 M solution in CH_2Cl_2, 0.18 mmol) was added to a solution of ethyl-3-{[(5-CBZ-amino)-2-phenyl-6-oxo-1,6-dihydro-l-pyrimidinyl]-L-*Gln*}-E-propenoate (0.050 g, 0.089 mmol) in trifluoroacetic acid (4 mL) at 23°C. The reaction mixture was stirred for 2 h at 23°C, then it was quenched with EtOH (2 mL) and concentrated. The residue was then partitioned between $NaHCO_3$ (50 mL) and EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford ethyl-3-{[(5-amino)-2-phenyl-6-oxo-l,6-dihydro-1-pyrimidinyl]-L-*Gln*}-E-propenoate (0.013 g, 36%) as a white solid: mp = 175°C (dec); IR (thin film) 3421, 1646 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.23 (t, 3H, J = 7.2 Hz), 1.62–1.64 (m, 1H), 1.71–1.78 (m, 1H), 2.01–2.06 (m, 2H), 4.13 (q, 2H, J = 7.2 Hz), 4.37–4.51 (m, 3H), 5.14 (bs, 1H), 5.79 (d, 1H, J = 15.6 Hz), 6.53–6.78 (m, 2H), 7.09–7.52 (m, 6H), 8.28 (d, 1H, J = 8.4 Hz).

Example 35 - Preparation of Compound 37: Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo [1,2-α]Pyrimidine-6-L-*Gln*]-E-Propenoate.

Preparation of Intermediate (S)-Pyrrolidin-2-one-5-Carboxylic Acid t-Butyl Ester.

To a suspension of L-pyroglutamic acid (2.00 g, 15.49 mmol) in t-butyl acetate was added 70% $HClO_4$ (0.46 mL, 17.04 mmol). The suspension was stirred at rt in a tightly closed flask overnight. The resulting solution was poured slowly into a sat. solution of $NaHCO_3$ and extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated to provide (S)-pyrrolidin-2-one-5-carboxylic acid t-butyl ester. (2.04 g, 85%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.16-2.48 (m, 4H), 4.14 (m, 1H), 5.97 (bs, 1H). MS calcd for $C_9H_{15}NO_3$+H 186, found 186.

Preparation of Intermediate (S)-Pyrrolidin-2-thione-5-Carboxylic Acid t-Butyl Ester.

To a solution of (S)-pyrrolidin-2-one-5-carboxylic acid t-butyl ester (2.04 g, 11.01 mmol) in benzene was added Lawesson's Reagent (2.22 g, 5.50 mmol). The reaction mixture was heated at reflux overnight, concentrated under vacuum, and purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to provide (S)-pyrrolidin-2-thione-5-carboxylic acid t-butyl ester (1.75 g, 79%) as a tan solid. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.30 (m, 1H), 2.53 (m, 1H), 2.85-3.04 (m, 2H), 4.42 (t, 1H, J = 7.7 Hz), 7.88 (bs, 1H). MS calcd for $C_9H_{15}NO_2S$+H 202, found 202.

Preparation of Intermediate (S)-2-Methylsulfanyl-3,4-Dihydro-5*H*-Pyrrole-5-Carboxylic Acid t-Butyl Ester.

To a solution of (S)-pyrrolidin-2-thione-5-carboxylic acid t-butyl ester (1.75 g, 8.71 mmol) in 35 mL of dry THF was added MeI (2.2 mL, 34.83 mmol) at rt. The mixture was stirred at rt for 3 h and concentrated under vacuum. CH_2Cl_2 was added to the resulting oil which was poured into a sat. solution of $NaHCO_3$. This was extracted 3 times with CH_2Cl_2, dried over $MgSO_4$, and concentrated to provide (S)-2-methylsulfanyl-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester (1.63 g, 87%) as a brown oil which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.09 (m, 1H), 2.28 (m, 1H), 2.48 (s, 3H), 2.56-2.80 (m, 2H), 4.59 (m, 1H). MS calcd for $C_{10}H_{17}NO_2S$+H, 216, found 216.

Preparation of Intermediate (S)-2-Amino-3,4-Dihydro-5*H*-Pyrrole-5-Carboxylic Acid t-Butyl Ester•HCl Salt.

To a solution of (S)-2-methylsulfanyl-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester (0.42 g, 1.95 mmol) in 4.0 mL anhydrous MeOH was added anh NH_4Cl (0.11 g, 2.05 mmol). The reaction mixture was heated to reflux for 2 h, concentrated in vacuo, and the residue was taken up in CH_2Cl_2. The white solids were filtered, and the filtrate was concentrated to provide (S)-2-amino-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester•HCl (0.41 g, 94%) as a light yellow solid· ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.24 (m, 1H), 2.52 (m, 1H), 3.06–3.08 (m, 2H), 4.44 (m, 1H), 9.81–9.84 (m, 2H). MS calcd for $C_9H_{16}N_2O_2$+H 185, found 185.

Preparation of Intermediate (S)-4-Oxo-4,6,7,8-Tetrahydropyrrolo [1,2-*a*] Pyrimidine- 3,6-Dicarboxylic Acid 6-t-Butyl Ester 3-Methyl Ester.

A solution of freshly prepared sodium methoxide (Na, 50 % by weight in paraffin, 0.084 g, 1.84 mmol, 2.25 mL anh MeOH) was added slowly to a solution of (S)-2-amino-3,4-dihydro-5*H*-pyrrole-5-carboxylic acid t-butyl ester•HCl (0.41 g, 1.84 mmol) in 2.25 mL anh MeOH cooled to -10°C. After 1 h, the resulting white precipitate (NaCl) was filtered, and the solution of this free base was slowly added to a solution of dimethylmethoxymethylene malonate (0.32 g, 1.84 mmol) in 2.25 mL anh MeOH at -10°C. The reaction mixture was stirred at 0°C overnight at which time it was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (2% MeOH/$CHCl_3$) to afford (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester 3-methyl ester (0.22 g, 40 %) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.31 (m, 1H), 2.57 (m, 1H), 3.09–3.33 (m, 2H), 3.90 (s, 3H), 5.03 (m, 1H), 8.69 (s, 1H). MS calcd $C_{14}H_{18}N_2O_5$+H 295, found 295.

Preparation of Intermediate (S)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-3,6-Dicarboxylic Acid 6-t-Butyl Ester.

To a solution of (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester 3-methyl ester (0.22 g, 0.74 mmol) in MeOH cooled to 0°C was added 2N NaOH (0.37 mL, 0.74 mmol) dropwise. The reaction mixture was allowed

to warm slowly to rt and stirred overnight. The reaction mixture was washed twicewith Et_2O, and the aqueous layer was acidified to pH 2 with 1N HC1, which was then extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to provide (S)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester (0.14 g, 70%) as a solid yellow foam ^{1}H NMR ($CDC1_3$) δ 1.50 (s, 9H), 2.41 (m, 1H), 2.68 (m, 1H), 3.21–3.41 (m, 2H), 5.10 (m, 1H), 8.94 (s, 1H). MS calcd $C_{13}H_{16}N_2O_5$+H, 281, found 281.

Preparation of Intermediate (S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-6-Carboxylic Acid t-Butyl Ester.

(S)-4-Oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-3,6-dicarboxylic acid 6-t-butyl ester (0.58 g, 2.07 mmol), triethylamine (0.29 mL, 2.07 mmol) and diphenylphosphoryl azide (0.45 mL, 2.07 mmol) in 1,4-dioxane (10 mL) were heated to reflux for 2 h. Benzyl alcohol (0.24 mL, 2.28 mmol) was added and heating at reflux was continued for another 3 h. The reaction mixture was then concentrated under vacuum, and the residue was purified by column chromatography on silica gel (2% MeOH/$CHC1_3$) to provide (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid t-butyl ester (0.62 g, 77%) as a yellow solid. ^{1}H NMR ($CDC1_3$) δ 1.48 (s, 9H), 2.30 (m, 1H), 2.56 (m, 1H), 3.05–3.21 (m, 2H), 4.98 (m, 1H), 5.20 (s, 2H), 7.30–7.40 (m, 6H), 8.67 (bs, 1H). MS calcd for $C_{20}H_{23}N_3O_5$+H, 386, found 386.

Preparation of Intermediate (S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo-[1,2-*a*]Pyrimidine-6-Carboxylic Acid.

To (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid t-butyl ester (0.20 g, 0.52 mmol) was added 8.0 mL of a 1:1 solution of TFA:$CHC1_3$ with 3 drops of H_2O. The reaction mixture was stirred at rt overnight, at which time it was concentrated under vacuum. $CC1_4$ was added, and the mixture was reconcentrated, and then triturated in Et_2O. Filtration provided (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid (0.14 g, 82%) as a tan solid ^{1}H NMR ($CDC1_3$) δ 2.50–2.63 (m, 2H), 3.16–3.29 (m, 2H), 5.13 (m, 1H), 5.20 (s, 2H), 5.45 (bs, 1H), 7.37 (s, 5H), 7.40 (s, 1H), 8.70 (bs, 1H). MS calcd for $C_{16}H_{15}N_3O_5$+H 330, found 330.

Preparation of Intermediate Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo[1,2-*a*]Pyrimidine-6-L-(Tr-*Gln*)]-E-Propenoate.

Ethyl-3-[BOC-L-(Tr-*Gln*)]-E-propenoate (0.28 g, 0.52 mmol) was deprotected and coupled to (S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-carboxylic acid (0.14 g, 0.41 mmol) using the procedure described in Example 1 for the preparation of ethyl-3-[BOC-L-N-Me-Phe-L-(Tr-*Gln*)]-E-propenoate, to provide ethyl-3-[(S)-3-(CBZ-amino)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-6-L-(Tr-*Gln*)]-E-propenoate (0.26 g, 83%) as a solid white foam after column chromatography (2% methanol/$CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 1.83 (m, 1H), 2.01 (m, 1H), 2.29–2.36 (m, 2H), 2.49–2.51 (m, 2H), 2.97 (m, 1H), 3.19 (m, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.53–4.57 (s, 2H), 5.86 (dd, 1H, J = 15.6, 1.6 Hz), 6.79 (dd, 1H, J = 15.6, 5.3 Hz), 6.89 (s, 1H), 7.16–7.37 (m, 21H), 7.53 (d, 1H, J = 7.2 Hz), 8.65 (bs, 1H)•MS calcd for $C_{44}H_{43}N_5O_7$+Cs, 886, found 886.

Preparation of Product-Ethyl-3-[(S)-3-(CBZ-Amino)-4-Oxo-4,6,7,8-Tetrahydropyrrolo[1,2-*a*]Pyrimidine-6-L-*Gln*]-E-Propenoate.

Ethyl-3-[(S)-3-(CBZ-amino)-4-oxo- 4,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyrimidine-6-L-(Tr-*Gln*)]-E-propenoate (0.25 g, 0.33 mmol) was deprotected using the procedure described in Example 22 for the preparation of ethyl-3-(ethylthiocarbonyl-L-Leu-L-Pro-L-*Gln*)-E-propenoate, to provide ethyl-3-[(S)-3-(CBZ-amino)-4-oxo4,6,7,8-tetrahydropyrrolo [1,2-*a*]pyrimidine-6-L-*Gln*]-E-propenoate (0.10 g, 59%) as a white solid after column chromatography on silica (5% methanol/$CHCl_3$): mp = 204 °C (dec.); IR (thin film) 3282 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 1.86 (m, 1H), 2.05 (m, 1H), 2.28–2.35 (m, 2H), 2.46–2.51 (m, 2H), 3.02 (m, 1H), 4.20 (q, 2H, J = 7.2 Hz), 4.62 (m, 1H), 5.00 (dd, 1H, J = 8.3, 3.6 Hz), 5.20 (s, 1H), 5.57 (m, 1H), 5.86 (m, 1H), 5.94 (dd, 1H, J = 15.5, 1.4 Hz), 6.84 (dd, 1H, J = 15.6, 5.2 Hz), 7.36–7.40 (m, 5H), 7.44 (s, 2H), 8.69 (m, 1H). HRMS calcd for $C_{25}H_{29}N_5O_7$+Cs 644.112, found 644.1143; Anal ($C_{25}H_{29}N_5O_7$) C, H, N.

The remaining compounds illustrated above can be produced by the skilled artisan, using routine experimentation, in a manner analogous to the various procedures described above in Examples 1 through 35.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Inhibition of Rhinovirus Protease

Stock solutions (50 mM, in DMSO) of various compounds were prepared; dilutions were in the same solvent. Recombinant Rhinovirus 3C proteases from serotypes 14, 16, 2 or 89 were prepared by the following standard chromatographic procedures: (1) ion exchange using Q Sepharose Fast Flow from Pharmacia; (2) affinity chromatography using Affi-Gel Blue from Biorad; and (3) sizing using Sephadex G-100 from Pharmacia. Assays contained 2% DMSO, 50 mM tris pH 7.6, 1 mM EDTA, a compound at the indicated concentrations, approximately 1μM substrate, and 50-100 nM protease. For K_i determinations, the compound and the enzyme were preincubated for 10 minutes at 30°C prior to addition of the substrate (substrate start). The $k_{obs/I}$ values were obtained from reactions initiated by addition of enzyme rather than substrate. RVP activity is measured in the fluorescence resonance energy transfer assay. The substrate was (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Phe-Gln-Gly-Pro-Val-Gly)-EDANS. In the uncleaved peptide, the EDANS fluorescence was quenched by the proximal DABCYL moiety. When the peptide was cleaved, the quenching was relieved, and activity was measured as an increase in fluorescence signal. Data was analyzed using standard non linear fitting programs (Enzfit), and are shown Table 1.

TABLE 1

COMPOUND	RVP	INHIB	$k_{obs/I}$ ($M^{-1}sec^{-1}$)
1		>100μM(K_i)	52
2		ND	5,300
	(2)	ND	617
	(16)	ND	1,035
3		12μM(K_i)	16,565
	(2)	ND	292
	(16)	ND	929
4		2.9μM(K_i)	43,800
	(2)	ND	541
	(16)	ND	2,009
5		ND	17,320

6		ND	9,500
7		ND	3,824
8		ND	6,885
9		4.4μM(K_i)	57,000
10		2.0μM(K_i)	41,800
11		ND	12,000
12		ND	5,070
13		ND	355,800
	(2)	ND	3,980
	(16)	ND	11,680
14		0.8μM(K_i)	56,400
	(2)	ND	800
	(16)	ND	1800
15		2.5μM(K_i)	36,400
	(2)	ND	3,500
	(16)	ND	5,600
16		12μM(K_i)	8,300
	(2)	ND	600
	(16)	ND	1,000
17		ND	750,000
18		7.0μM(K_i)	423
19		ND	1,927
20		62μM(K_i)	3,332
21		50μM(K_i)	256
22		ND	100
23		60μM(K_i)	605
24		8μM(K_i)	21,960
	(2)	ND	7,100
	(16)	ND	9,300
25		ND	1,469
	(2)	ND	1,277

	(16)	ND	770
26		34μM(Ki)	875
27		ND	102
	(2)	ND	87
	(16)	ND	90
28		50μM(K_i)	116
29		ND	45
30		55μM(K_i)	163
31		ND	39
32		ND	98
33		86(10)	361
34		ND	13,400
	(2)	ND	940
	(16)	ND	2,065
35		ND	22,500
	(2)	ND	1,600
	(16)	ND	3,480
36		ND	2,000
	(2)	ND	400
	(16)	ND	750
37		ND	12,400
	(2)	ND	2,500
	(16)	ND	4,000
38		ND	18,200
39		ND	2,330
40		ND	12,100
41		ND	2,350
42		ND	15,000
43		ND	2,200
44		ND	12,300
45		ND	2,300

46	ND	36,800
47	ND	6,500
48	ND	14,050
49	ND	1,910
50	ND	14,000
51	ND	43,900
52	ND	31,100
53	ND	242
54	55(10)	ND
55	20(10)	ND
56	ND	15,400
57	ND	13,500
58	ND	24,300
59	2.8	108,000

In the above table, all data is for RVP serotype-14 unless otherwise noted in parentheses. All strains of human rhinovirus (HRV) were purchased from American Type Culture Collection (ATCC), except for serotype 14, which was produced from the infectious cDNA clone constructed and supplied to us by Dr. Roland Rueckert at the Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. The column designated INHIB represents the percent inhibition, with the concentration of the compound in µM indicated in parentheses, unless K_i was assigned as designated by (K_i), at 10 minute preincubation with 50 nM RVP prior to addition of substrate was used. The data in the column designated $k_{obs/I}$ was measured from progress curves in enzyme start experiments. The designation NI indicates that no inhibition was obtained when 10 µM of a compound was used. The designation ND indicates that a value was not determined for that compound.

Antirhinoviral HI-HeLa Cell Culture Assay

In the Cell Protection Assay, the ability of compounds to protect cells against HRV infection was measured by the XTT dye reduction method. This method is described in O.S.

Weislow, R. Kiser, D.L. Fine, J. Bader, R.H. Shoemaker, and M.R. Boyd, *J. Natl. Cancer Inst.* 1989, 81, 577-586, which document is entirely incorporated herein by reference.

HI-HeLa cells were infected with HRV-14 (unless otherwise noted) at a multiplicity of infection (m.o.i.) of 0.13 (virus particles/cell) or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8 x 10^5 cells per mL and incubated with appropriate concentrations of compounds of formulas I and II. Two days later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free mock-infected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in compound-treated, mock-infected cells to 50% of that produced in compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

All strains of human rhinovims (HRV) for use in this assay were purchased from American Type Culture Collection (ATCC), except for HRV serotype-14, which was produced from the infectious cDNA clone, constructed and supplied to us by Dr. Roland Rueckert at the Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin. HRV stocks were propagated, and antiviral assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium, available from Life Technologies, with 10% fetal bovine serum.

The compounds were tested against control compounds WIN 51711, WIN 52084, and WIN 54954, all obtained from Sterling-Winthrop Pharmaceuticals, and control compound Pirodavir, obtained from Janssen Pharmaceuticals. Antiviral data obtained for the test compounds are shown in Table 2 where all data are for HRV serotype-14 unless otherwise noted in parentheses.

TABLE 2

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
1	20	251	13
2	1.0	56	56

3	0.18	41.7	232
4	0.23	200	870
5	0.24	51.4	214
6	2.8	151.4	54
7	1.3	47.9	37
8	10	>320	>32
9	0.25	56.2	225
10	1.8	56.2	31
11	0.53	>320	>603
12	4.2	>320	>76
13	0.12	17.8	148
14	0.32	15.8	49
15	0.26	50.1	192
16	1.7	32	19
17	0.5	53	106
18	5.0	126	25
19	50	>320	>6
20	5.4	56	10.3
21	22	>320	>15
22	177.8	>320	>2
23	10	224	22
24	10	>100	>10
25	14	>320	>23
26	56	>320	>5
27	>320	>320	
28	6.9	125	18
29	46	251	5
30	7.2	177	25
31	56	>320	>6

32	158	>320	>2
33	>320	>320	
34	0.32	>100	>312
35	0.19	>100	>526
36	11.2	>100	>9
37	8.9	>100	>11
38	0.36	>100	>278
39	1.6	180	113
40	0.32	45	141
41	2.0	18	9
42	0.45	50.1	111
43	3.5	56.2	16
44	0.54	56.2	104
45	1.78	56.2	32
46	0.54	18	33
47	1.3	18	14
48	0.5	>10	>20
49	0.1	71	710
50	3.2	>100	>31
51	12.6	>100	>8
52	32	>100	>3
53	4.5	>100	>22
54	17.8	>100	>6
55	50	>100	>2
56	1.6	20	13
57	0.56	50	89
58	0.56	63	113
59	0.14	>100	>714
59 (HRV 1A)	0.40	>100	>250

59 (HRV 10)	0.40	>100	>250
WIN 51711	0.78	>60	>77
WIN 52084	0.07	>10	>143
WIN 54954	2.13	>63	>30
Pirodavir	0.03	>10	>300

Anticoxsackieviral Hi HeLa Cell Culture Assay

The ability of compounds to protect cells against CVA-21 or CVB-3 infection was measured by the XTT dye reduction method. Briefly, HI-HeLa cells were infected with CVA-21 or CVB-3 at a multiplicity of infection (m.o.i.) of 0.05 (CVA-21) and 0.08 (CVB-3) or mock-infected with medium only. Infected or uninfected cells were resuspended at 4 x 10^4 cells per mL and incubated with appropriate concentrations of drug. One day later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of drug that increased the percentage of formazan production in drug-treated, virus-infected cells to 50% of that produced by drug-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of drug that decreased the percentage of formazan produced in drug-treated, uninfected cells to 50% of that produced in drug-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

The Coxsackie strains A-21 (CVA-21) and B-3 (CVB-3) were purchased from American Type Culture Collection (ATCC). Virus stocks were propagated and antiviral assays were performed in HI-HeLa cells (ATCC). Cells were grown in Minimal Essential Medium with 10% fetal bovine serum.

Table 3. Antiviral efficacy of compounds against CVB-3 infection of Hi-HeLa cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	2.0	56	28
WIN 54954	>100	>100	

Pirodavir	>100	>100

Table 4. Antiviral efficacy of compounds against CVA-21 infection of Hi-HeLa cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	3.3	56	17
4	1.8	200	111
WIN 54954	>100	>100	
Pirodavir	>100	>100	

Echovirus-11 and Enterovirus-70 MRC5 Cell Culture Assay

The Echovirus strain 11 (ECHO-11) and Enterovirus strain 70 (ENT-70) were purchased from American Type Culture Collection (ATCC). Virus stocks were propagated and antiviral assays were performed in MRC5 cells (ATCC). Cells were grown in Minimal Essential Medium with 10% fetal bovine serum.

The ability of compounds to protect cells against ECHO-11 or ENT-70 infection was measured by the XTT dye reduction method. Briefly, MRC5 cells were infected with ECHO-11 or ENT-70 at a multiplicity of infection (m.o.i.) of 0.0013 (ECHO-11) and 0.0017 (ENT-70) or mock-infected with medium only. Infected or uninfected cells were resuspended at 2 x 10^4 cells per mL and incubated with appropriate concentrations of drug. One day later, XTT /PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC_{50} was calculated as the concentration of drug that increased the percentage of formazan production in drug-treated, virus-infected cells to 50% of that produced by drug-free, uninfected cells. The 50% cytotoxic dose (CC_{50}) was calculated as the concentration of drug that decreased the percentage of formazan produced in drug-treated, uninfected cells to 50% of that produced in drug-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC_{50} by the EC_{50}.

Table 5. Antiviral efficacy of compounds against ECHO-11 infection of MRC5 cells.

Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI

2	3.1	56	18
4	3.2	200	62.5
WIN 54954	>100	>100	
Pirodavir	>100	>100	

Table 6. Antiviral efficacy of compounds against ENT-70 infection of MRC5 cells.

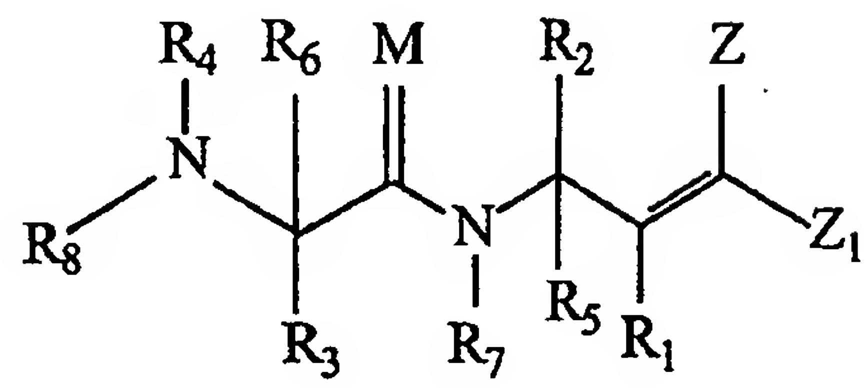
Compound #	$EC_{50}(\mu M)$	$CC_{50}(\mu M)$	TI
2	0.6	56	93
4	0.3	200	667
WIN 54954	>100	>100	
Pirodavir	>100	>100	

In describing the invention, the inventors have set forth certain theories and mechanisms in an effort to disclose how or why the invention works in the manner in which it works. These theories and mechanisms are set forth for informational purposes only. Applicants are not to be bound by any specific chemical or physical mechanisms or theories of operation.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof. Thus, it is intended that the present invention cover the modifications and variations, provided they come within the scope of the appended claims and their equivalents.

WE CLAIM:

1. A compound of formula (I):



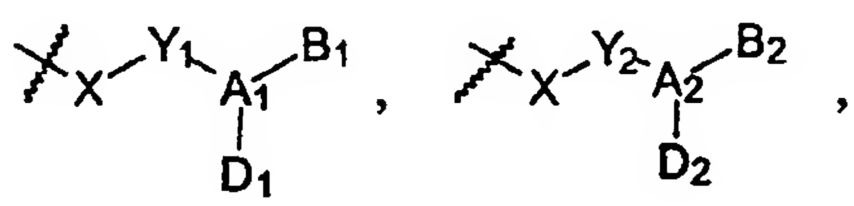
(I),

wherein:

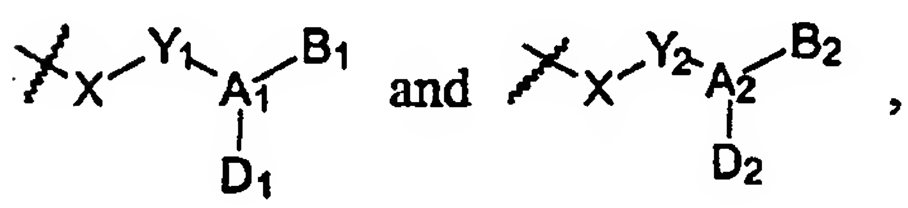
M is O or S;

R_1 is H, F, an alkyl group, OH, SH, or an O-alkyl group;

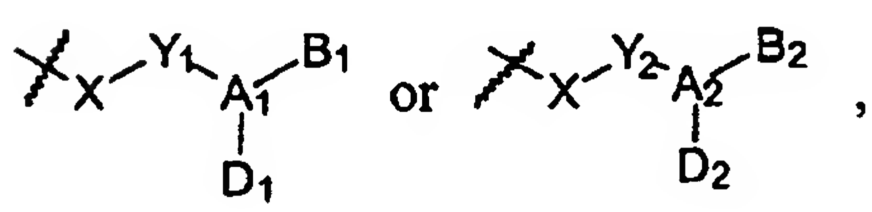
R_2 and R_5 are independently selected from H,



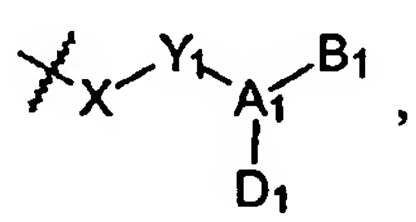
or an alkyl group, wherein said alkyl group is different from



with the proviso that at least one of R_2 or R_5 must be



and wherein, when R_2 or R_5 is



X is =CH or =CF and Y_1 is =CH or =CF,

or X and Y_1 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or -O-, X is -CH- or -CF-, and Y is -CH-, -CF-, or -C(alkyl)-,

where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_1 is $-O-$, $-S-$, $-NR_{12}-$, $-C(R_{13})(R_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR_{13}R_{14})-$,

wherein R_{12} is H or alkyl, and R_{13} and R_{14} independently are H, F, or an alkyl group, or, together with the atoms to which they are bonded, form a cycloalkyl group or a heterocycloalkyl group;

A_1 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom to which they are bonded, form a heterocycloalkyl group;

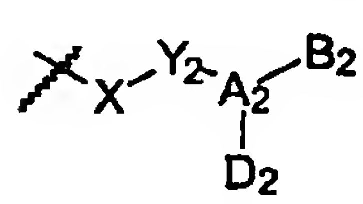
D_1 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and B_1 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and with the provisos that when D_1 is the moiety $\equiv N$ with a lone pair of electrons capable of forming a hydrogen bond, B_1 does not exist; and when A_1 is an sp^3 carbon, B_1 is not $-NR_{17}R_{18}$ when D_1 is the moiety $-NR_{25}R_{26}$ with a lone pair of electrons capable of forming a hydrogen bond, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

and wherein $D_1-A_1-B_1$ optionally forms a nitro group where A_1 is N;

and further wherein, when R_2 or R_5 is



,

X is $=CH$ or $=CF$ and Y_2 is $=C$, $=CH$ or $=CF$,

or X and Y_2 together with Q' form a three-membered ring in which Q' is $-C(R_{10})(R_{11})-$ or $-O-$, X is $-CH-$ or $-CF-$, and Y_2 is $-CH-$, $-CF-$, or $-C(alkyl)-$, where R_{10} and R_{11} independently are H, a halogen, or an alkyl group, or, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group,

or X is $-CH_2-$, $-CF_2-$, $-CHF-$, or $-S-$, and Y_2 is $-O-$, $-S-$, $-N(R'_{12})-$, $-C(R'_{13})(R'_{14})-$, $-C(O)-$, $-C(S)-$, or $-C(CR'_{13}R'_{14})-$,

wherein R'_{12} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR'_{13}$, $-NR'_{13}R'_{14}$, $-C(O)-R'_{13}$, $-SO_2R'_{13}$, or $-C(S)R'_{13}$, and R'_{13} and R'_{14}, independently are H, F, or an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group;

A_2 is C, CH, CF, S, P, Se, N, NR_{15}, S(O), Se(O), $P-OR_{15}$, or $P-NR_{15}R_{16}$,

wherein R_{15} and R_{16} independently are an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group or, together with the atom to which they are bonded, form a heterocycloalkyl group;

D_2 is a moiety with a lone pair of electrons capable of forming a hydrogen bond; and B_2 is H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

and further wherein any combination of Y_2, A_2, B_2, and D_2 forms a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

R_3 and R_6 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{17}$, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or, R_3 and R_6, together with the carbon atom to which they are attached, form a cycloalkyl group or a heterocycloalkyl group; R_4 is any suitable organic moiety, or R_4 and R_3 or R_6, together with the atoms to which they are attached, form a heterocycloalkyl group;

R_7 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-OR_{17}$, $-SR_{17}$, $-NR_{17}R_{18}$, $-NR_{19}NR_{17}R_{18}$, or $-NR_{17}OR_{18}$,

wherein R_{17}, R_{18}, and R_{19} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group;

or R_7, together with R_3 or R_6 and the atoms to which they are attached, forms a heterocycloalkyl group;

R_8 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-NR_{29}R_{30}$, $-OR_{29}$, or $-C(O)R_{29}$,

wherein R_{29} and R_{30} each independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group;

or R_8, together with R_4 and the nitrogen atom to which they are attached, forms a heterocycloalkyl group or a heteroaryl group, or R_8 and R_3 or R_6, together with the atoms to which they are attached, forms a heterocycloalkyl group;

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{23})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group;

or Z_1, as defined above, together with R_1, as defined above, and the atoms to which Z_1 and R_1 are bonded, form a cycloalkyl or heterocycloalkyl group,

or Z and Z_1, both as defined above, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group;

with the proviso that when R_7 is H, R_8 is a moiety other than H;

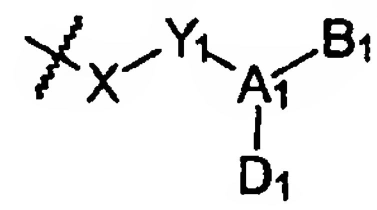
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof;

and wherein said compound, pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof has antipicornaviral activity with an EC_{50} less than or equal to 100 µM in the HI-HeLa cell culture assay.

2. A compound of claim 1, wherein R_1 is H or F, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

3. A compound of claim 1, wherein at least one of R_4 and R_8 is an acyl group or a sulfonyl group, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

4. A compound of claim 1, wherein at least one of R_2 or R_5 is



,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

5. A compound according to claim 4, wherein D_1 is $-OR_{25}$, =O, =S, ≡N, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the nitrogen atom to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

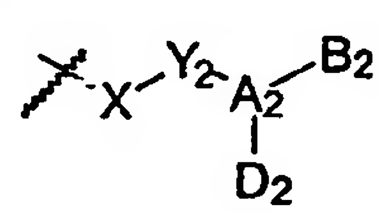
6. A compound according to claim 5, wherein D_1 is =O; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

7. A compound according to claim 4, wherein A_1 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

8. A compound according to claim 7, wherein A_1 is C; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

9. A compound according to claim 4, wherein B_1 is $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

10. A compound according to claim 1, wherein at least one of R_2 or R_5 is



,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

11. A compound according to claim 10, wherein D_2 is $-OR_{25}$, =O, =S, ≡N, $=NR_{25}$, or $-NR_{25}R_{26}$, wherein R_{25} and R_{26} are independently H, an alkyl group, a cycloalkyl group

group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, or, together with the atom(s) to which they are bonded, form a heterocycloalkyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

12. A compound according to claim 11, wherein D_2 is =O; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

13. A compound according to claim 10, wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

14. A compound according to claim 13, wherein A_2 is C; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

15. A compound according to claim 10, wherein B_2 is $NR_{17}R_{18}$, wherein R_{17} and R_{18} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

16. A compound according to claim 1, wherein A_1 is C, CH, S, or S(O) or wherein A_2 is C, CH, S, or S(O); or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

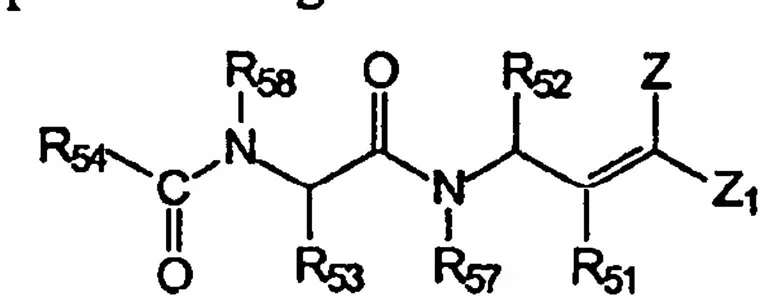
17. A compound according to claim 1, wherein Z and Z_1 are independently H, an aryl group, or a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$ $-SO(NR_{21})(OR_{22})$, $SONR_{21}$, $-SO_3R_{21}$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$;

wherein R_{21}, R_{22}, and R_{23} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, and R_{23}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

18. A compound according to claim 1, wherein M is O, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

19. A compound having the formula II:

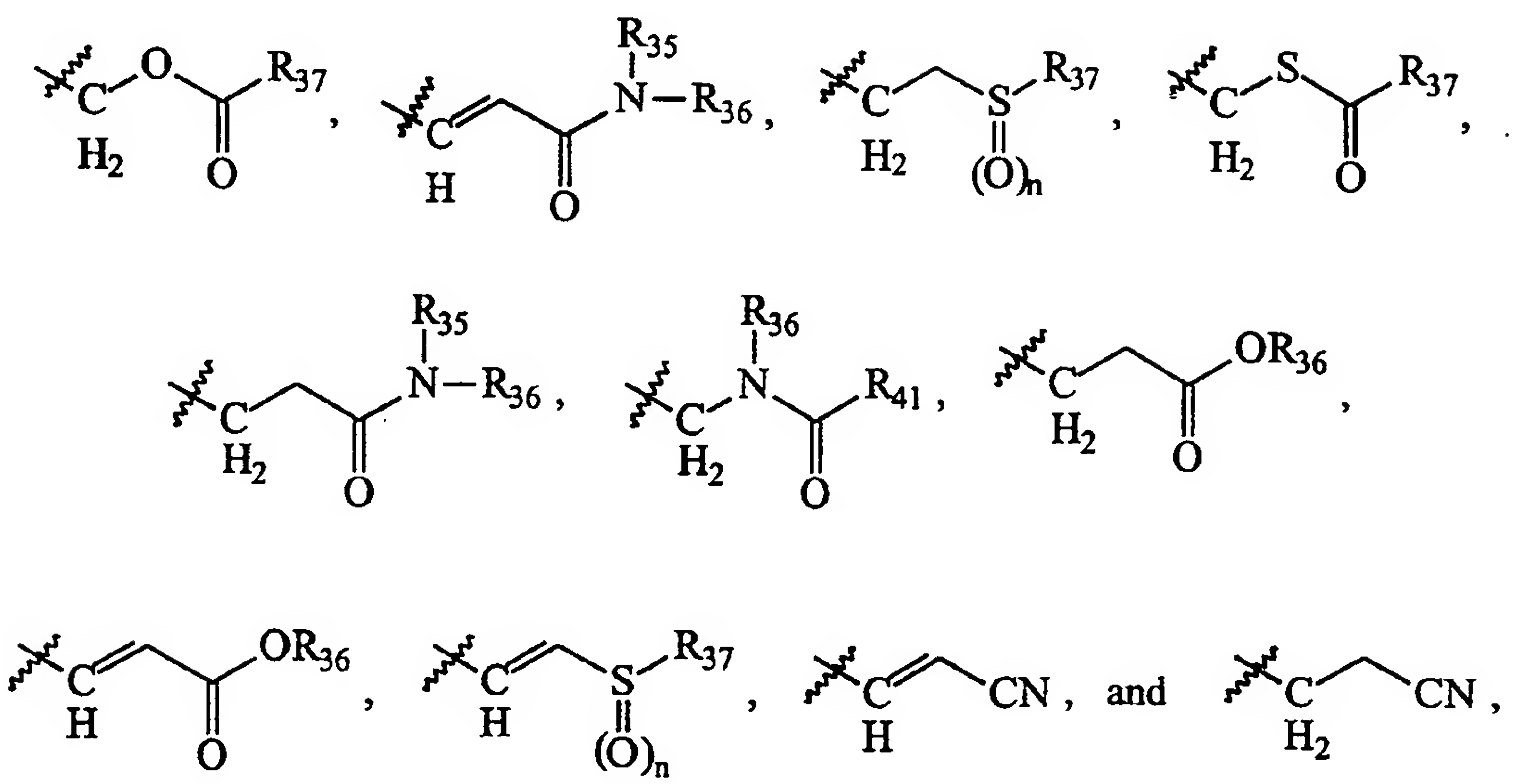


(II),

wherein:

R_{51} is H, F, or an alkyl group;

R_{52} is selected from one of the following moieties:



wherein:

R_{35} is H, an alkyl group, an aryl group, $-OR_{38}$, or $-NR_{38}R_{39}$,

wherein R_{38} and R_{39} independently are H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

R_{36} is H or an alkyl group,

or R_{35} and R_{36}, together with the nitrogen atom to which they are attached, form a heterocycloalkyl group or a heteroaryl group;

R_{37} is an alkyl group, an aryl group, or $-NR_{38}R_{39}$, wherein R_{38} and R_{39} are as defined above;

R_{41} is H, an alkyl group, an aryl group, $-OR_{38}$, $-SR_{39}$, $-NR_{38}R_{39}$, $-NR_{40}NR_{38}R_{39}$, or $-NR_{38}OR_{39}$, or R_{41} and R_{36}, together with the atoms to which they are attached, form a heterocycloalkyl group, and

wherein R_{38} and R_{39} are as defined above and R_{40} is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or an acyl group; and

n is 0, 1 or 2;

R_{53} is H or an alkyl group;

R_{54} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an O-alkyl group, an O-cycloalkyl group, an O-heterocycloalkyl group, an O-aryl group, an O-heteroaryl group, an S-alkyl group, an NH-alkyl group, an NH-aryl group, an N,N-dialkyl group, or an N,N-diaryl group;

or R_{54}, together with R_{58} and the nitrogen atom to which they are attached, forms a heterocycloalkyl group or a heteroaryl group;

R_{57} is H or an alkyl group;

R_{58} is H, an alkyl group, a cycloalkyl group, $-OR_{70}$ or $-NR_{70}R_{71}$ wherein R_{70} and R_{71} are independently H or an alkyl group; and

Z and Z_1 are independently H, F, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $-C(O)R_{21}$, $-CO_2R_{21}$, $-CN$, $-C(O)NR_{21}R_{22}$, $-C(O)NR_{21}OR_{22}$, $-C(S)R_{21}$, $-C(S)NR_{21}R_{22}$, $-NO_2$, $-SOR_{21}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, $-SO(NR_{21})(OR_{22})$, $-SONR_{21}$, $-SO_3R_{21}$, $-PO(OR_{21})_2$, $-PO(R_{21})(R_{22})$, $-PO(NR_{21}R_{22})(OR_{22})$, $-PO(NR_{21}R_{22})(NR_{23}R_{24})$, $-C(O)NR_{21}NR_{22}R_{23}$, or $-C(S)NR_{21}NR_{22}R_{23}$,

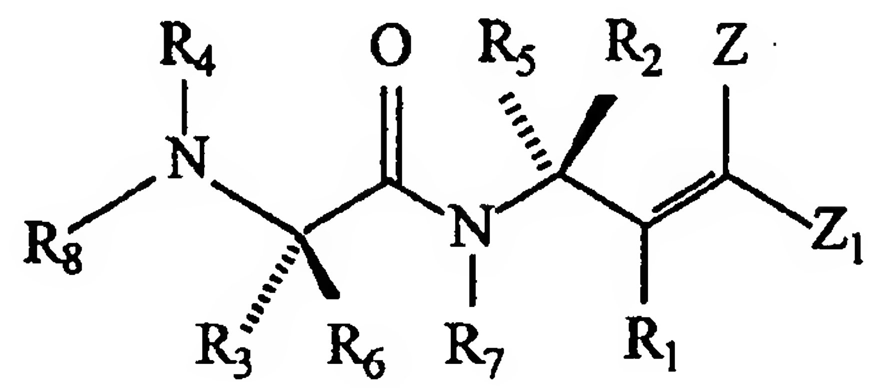
wherein R_{21}, R_{22}, R_{23}, and R_{24} are independently H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an acyl group, or a thioacyl group, or wherein any two of R_{21}, R_{22}, R_{23}, and R_{24}, together with the atom(s) to which they are bonded, form a heterocycloalkyl group,

or wherein Z and Z_1, together with the atoms to which they are bonded, form a heterocycloalkyl group;

with the proviso that when R_{57} is H, R_{58} is a moiety other than H;

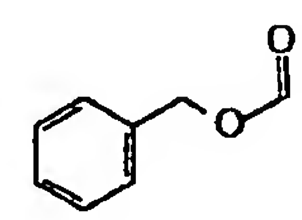
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

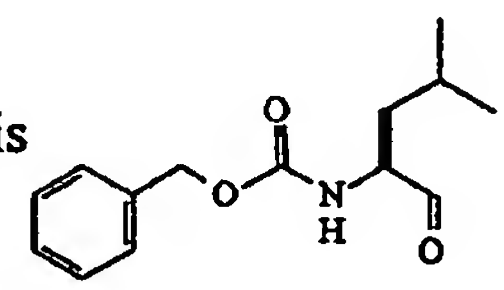
20. A compound according to claim 1, having the formula Ia:

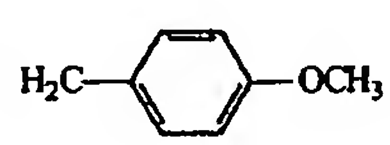
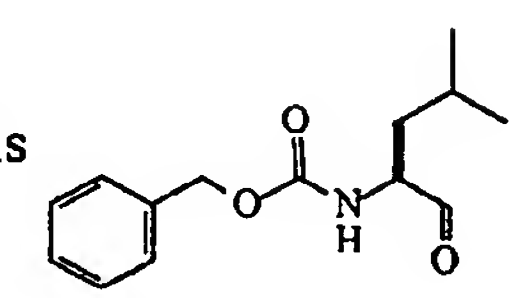


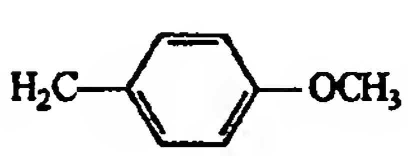
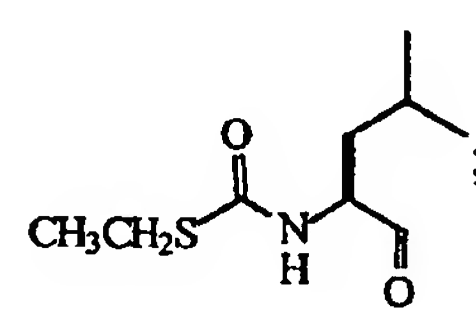
(Ia),

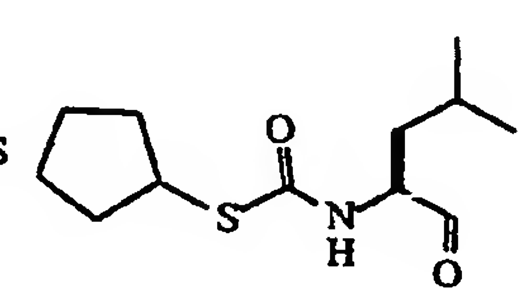
wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

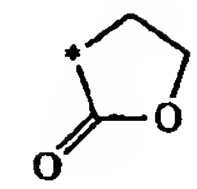
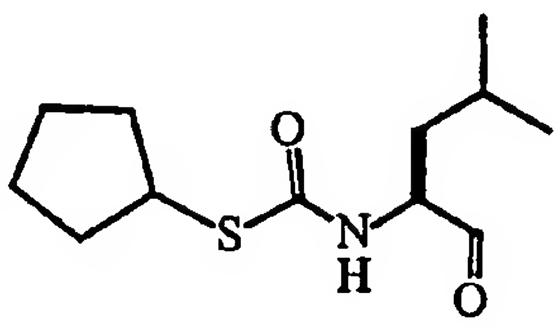
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

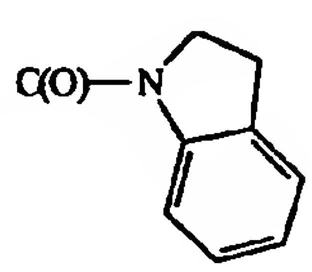
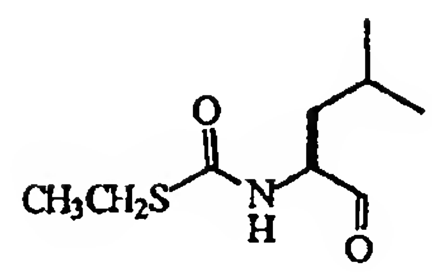
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

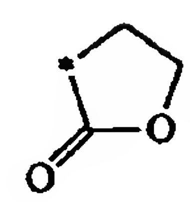
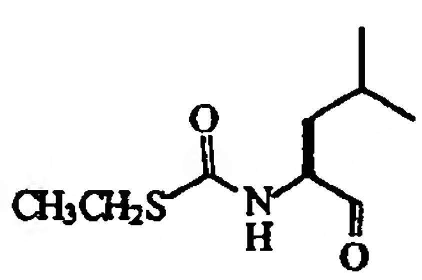
Z is H, Z_1 is $CO_2CH_2CH_3$, R_3 is  , and R_8 is  ;

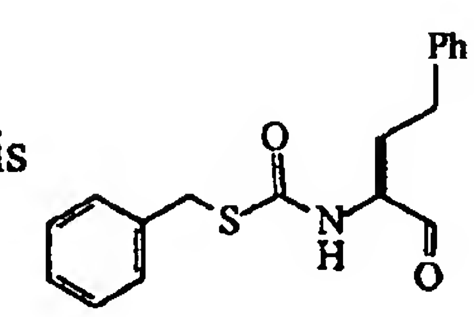
R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

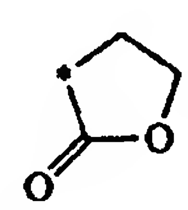
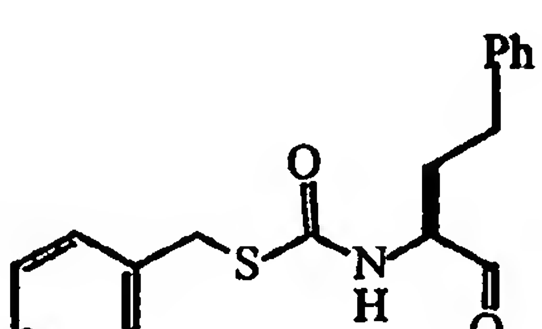
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

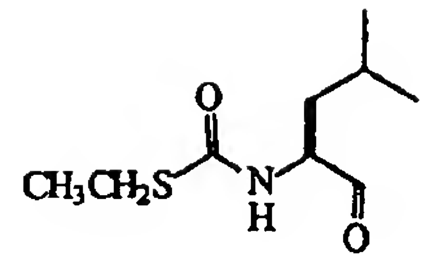
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O is cis to the R_1 group), and R_8 is ;

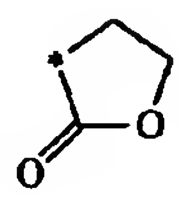
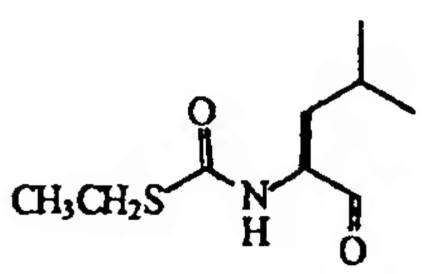
R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is ;

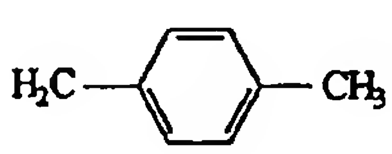
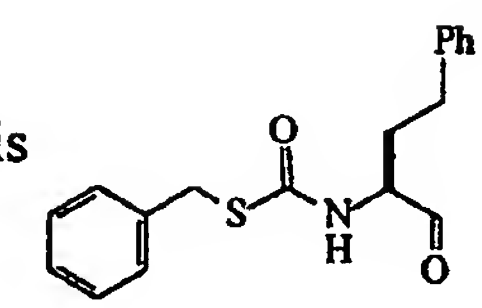
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is ;

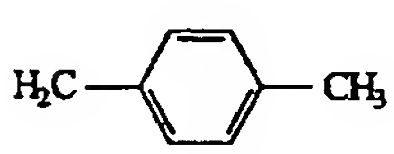
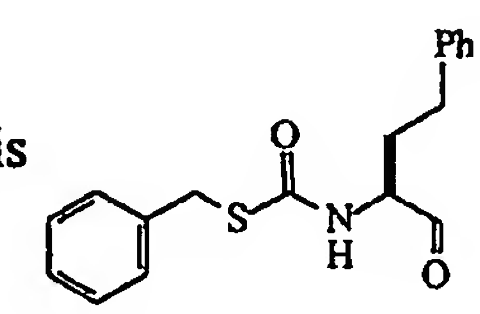
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is ;

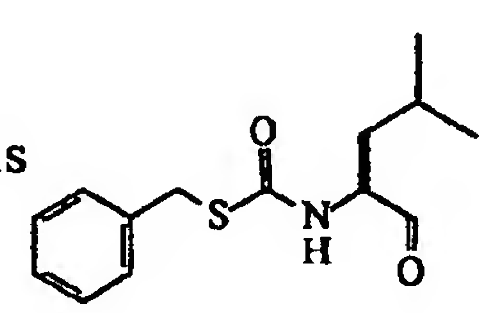
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is ;

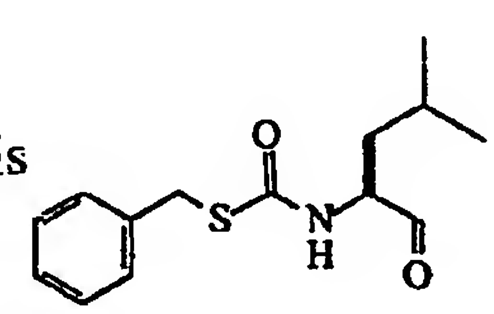
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

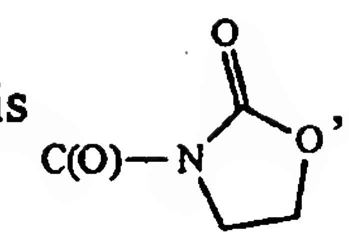
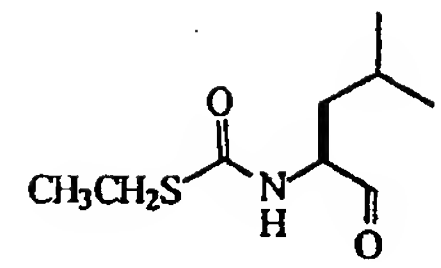
R_3 is CH_2Ph, Z and Z_1 together form  (wherein the C=O group is cis to the R_1 group), and R_8 is  ;

R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is  , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

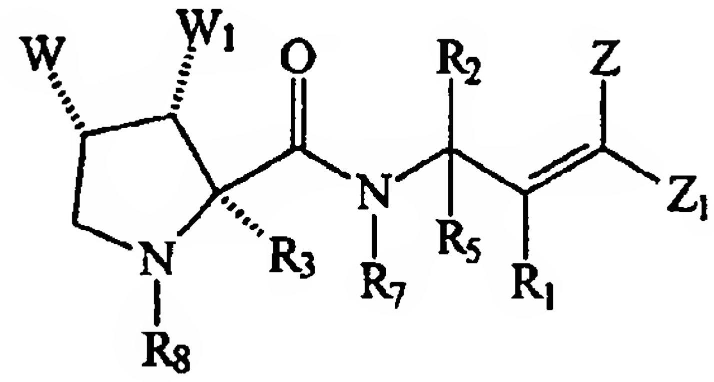
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ; and

R_3 is CH_2Ph, Z is H, Z_1 is , and R_8 is ,

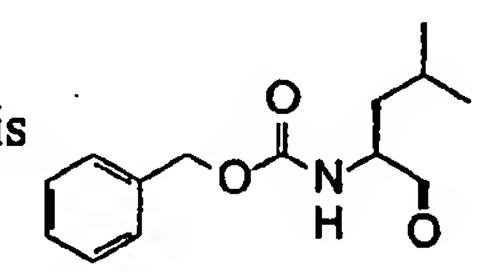
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

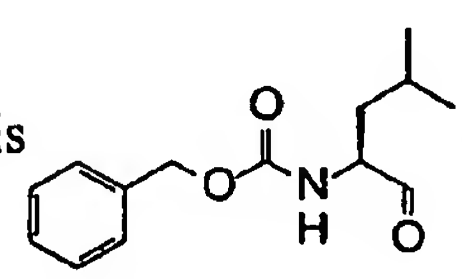
21. A compound according to claim 1, having the formula Ib:

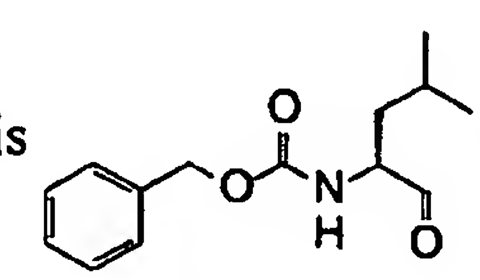


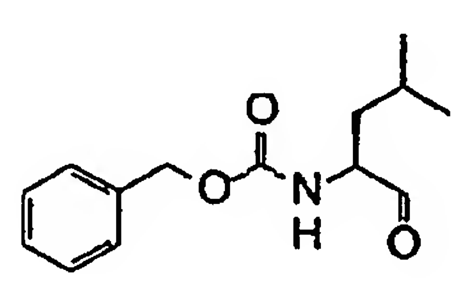
(Ib),

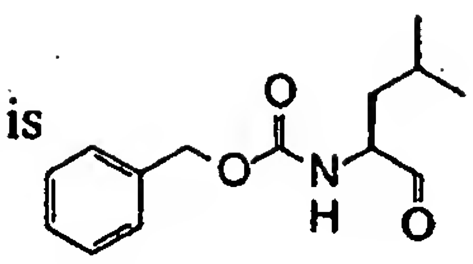
wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, and Z_1, W, W_1, and R_8 are selected from one of the following groups:

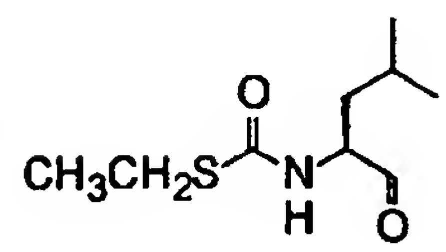
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is Ph, and R_8 is ;

Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is ;

Z_1 is $CO_2CH_2CH_3$, W is OCH_2Ph, W_1 is H, and R_8 is ;

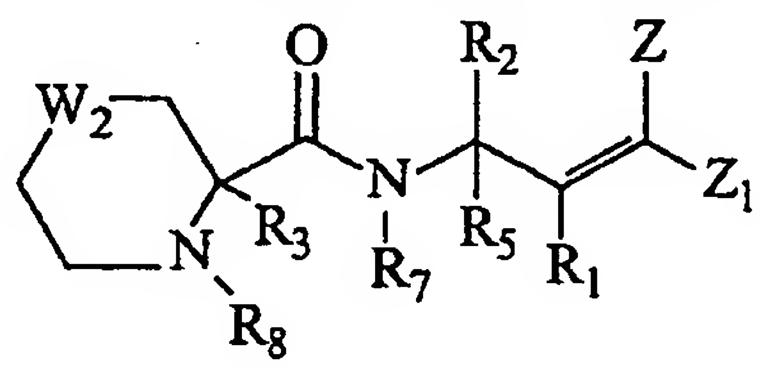
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is CH_3, and R_8 is ;

Z_1 is $CO_2CH_2CH_3$, W is $OC(CH_3)_3$, W_1 is H, and R_8 is  ; and

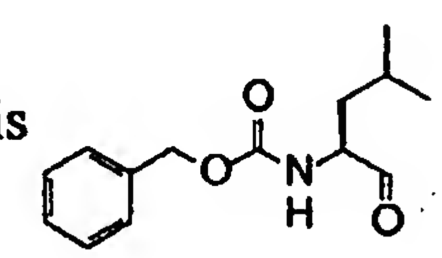
Z_1 is $CO_2CH_2CH_3$, W is H, W_1 is H, and R_8 is  ,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

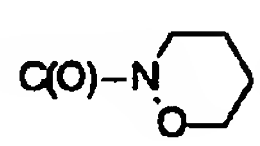
22. A compound according to claim 1, having the formula Ic:



(Ic),

wherein R_1, R_3, R_5, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_8 is  , and W_2 and Z_1 are selected from one of the following groups:

W_2 is CH_2 and Z_1 is $CO_2CH_2CH_3$;

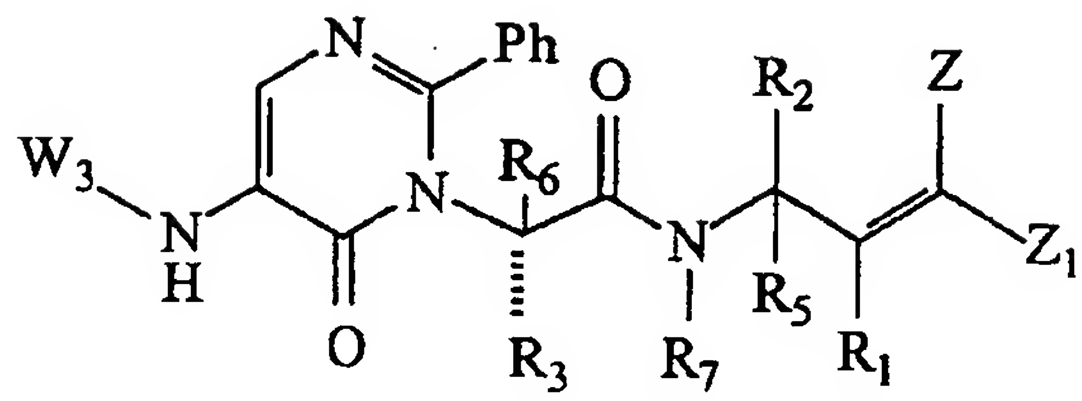
W_2 is CH_2 and Z_1 is  ;

W_2 is NCH_2Ph and Z_1 is $CO_2CH_2CH_3$; and

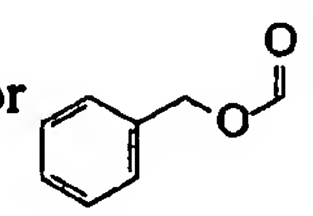
W_2 is NSO_2Ph and Z_1 is $CO_2CH_2CH_3$,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

23. A compound according to claim 1, having the formula Id:

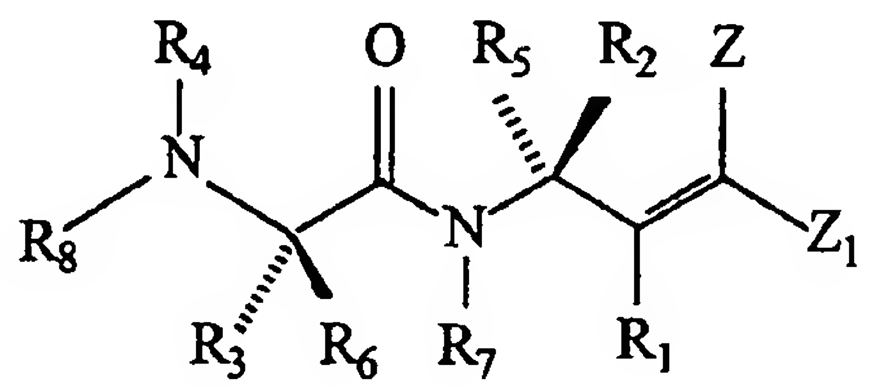


(Id),

wherein R_1, R_3, R_5, R_6, R_7, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_3 is H or  ,

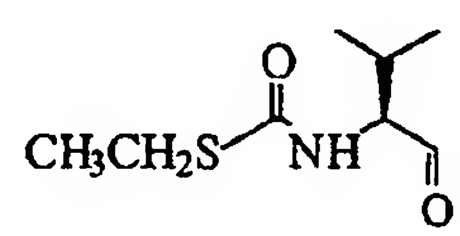
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

24. A compound according to claim 1, having the formula Ia:

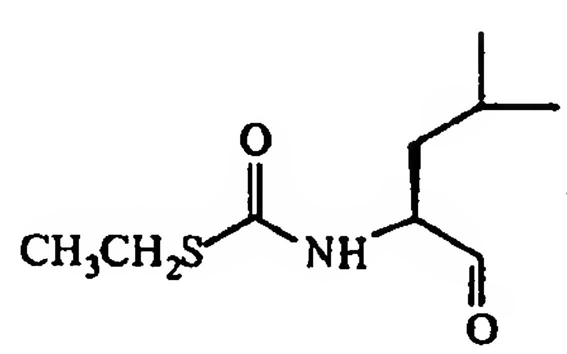


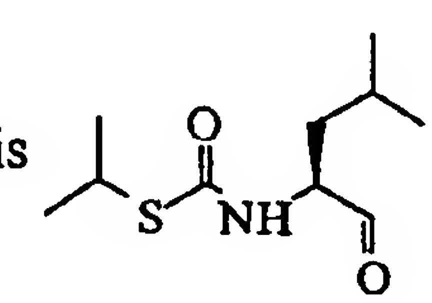
(Ia),

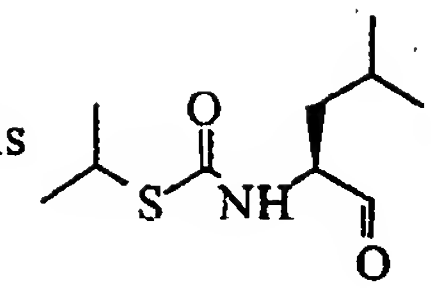
wherein R_1, R_5, R_6, and R_7 are each H, R_2 is $CH_2CH_2C(O)NH_2$, R_4 is CH_3, and R_3, Z, Z_1, and R_8 are selected from one of the following groups:

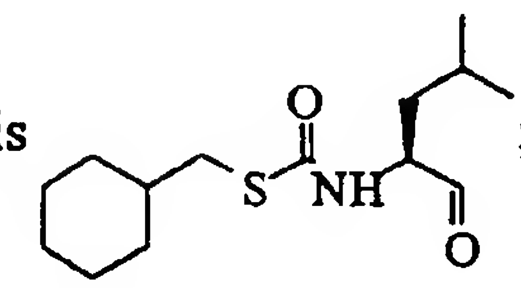
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

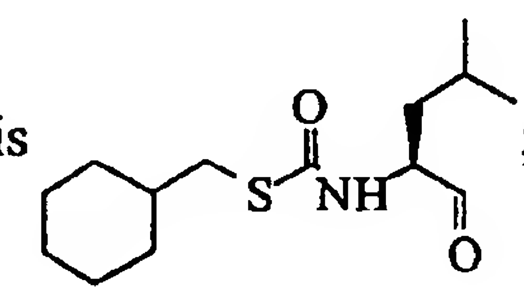
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

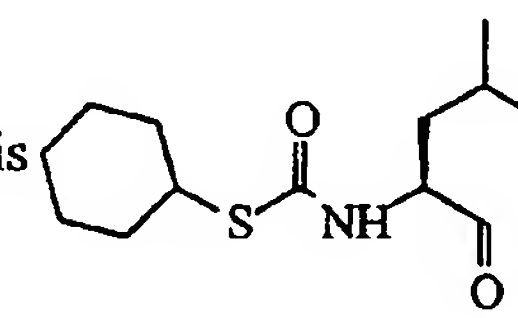
R_3 is CH_2Ph, Z is H, Z_1 is $C(O)N(CH_3)OCH_3$, and R_8 is  ;

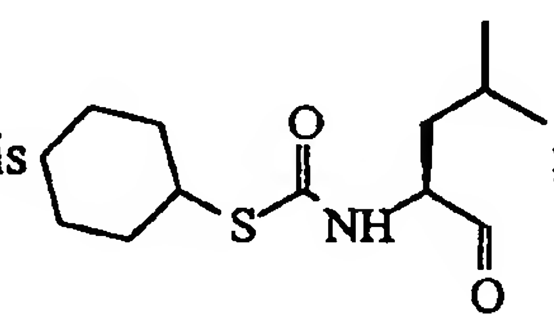
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

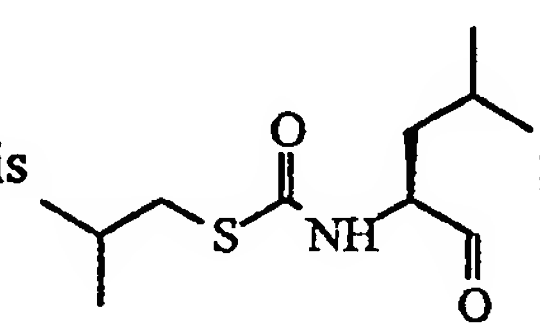
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R is  ;

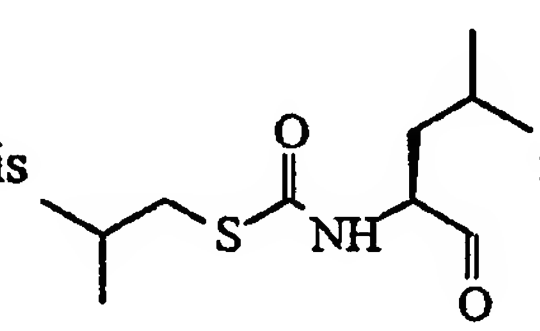
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

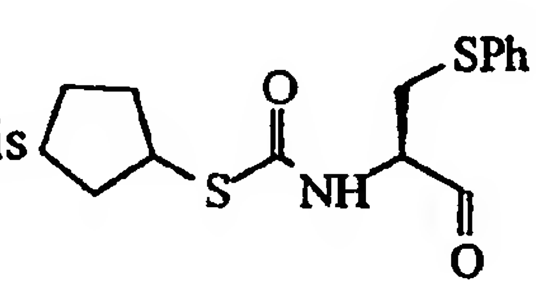
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

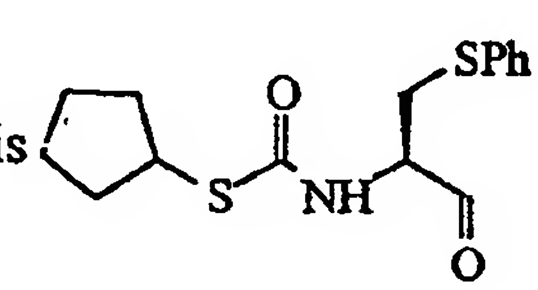
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

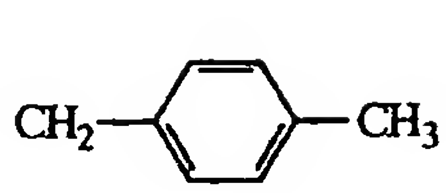
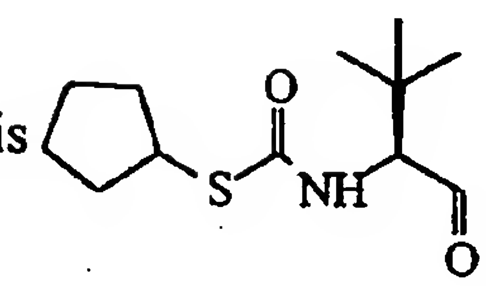
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

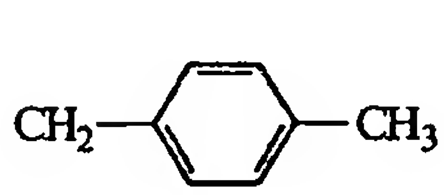
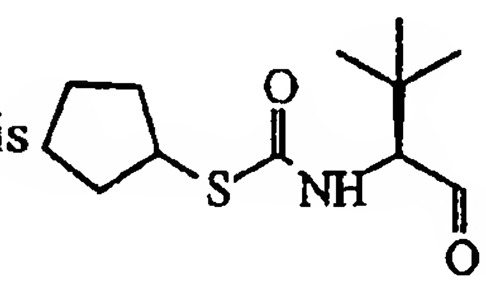
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

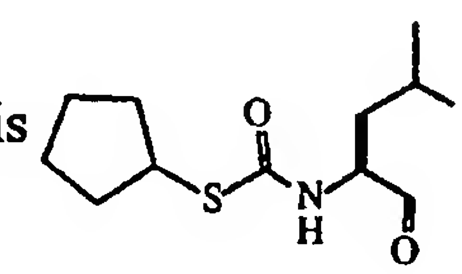
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

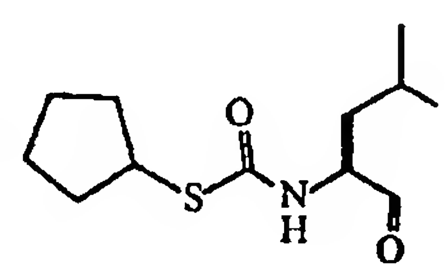
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

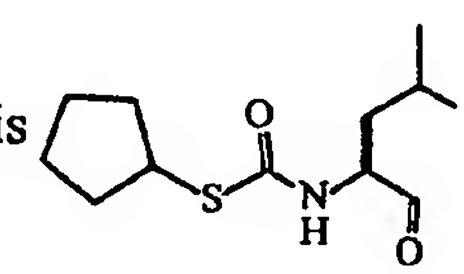
R_3 is CH_2Ph, Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is  , Z is H, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

R_3 is  , Z is CH_3, Z_1 is $CO_2CH_2CH_3$, and R_8 is  ;

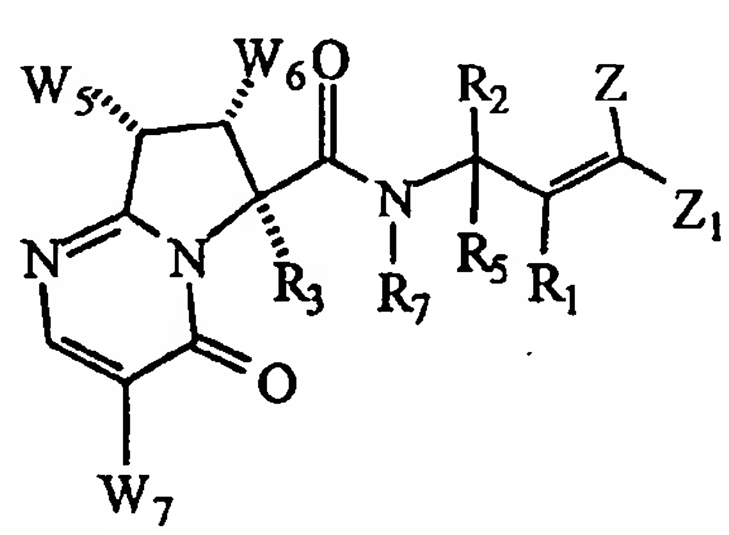
R_3 is CH_2Ph, Z is H, Z_1 is CO_2CH_2Ph, and R_8 is  ;

R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2CH_3$, and R_8 is  ; and

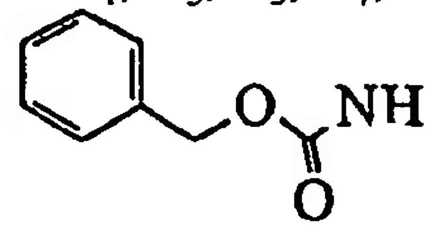
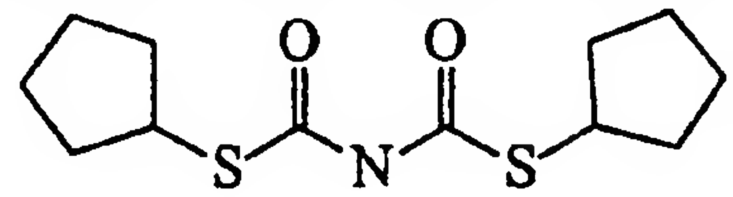
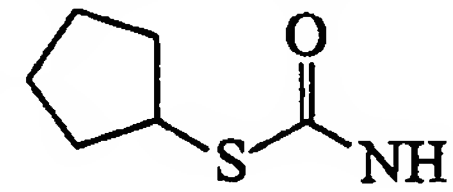
R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_2OCH_3$, and R_8 is  ,

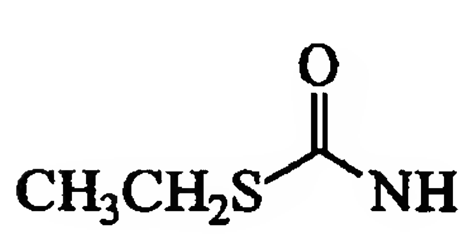
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

25. A compound according to claim 1, having the formula Ig:



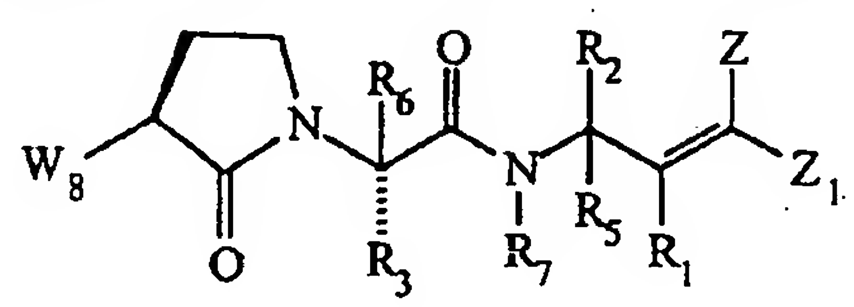
(Ig),

wherein R_1, R_3, R_5, R_7, W_5, W_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, Z_1 is $CO_2CH_2CH_3$, and W_7 is  ,  ,  , or

 ,

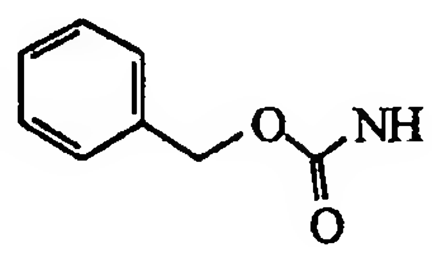
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

26. A compound according to claim 1, having the formula Ih:



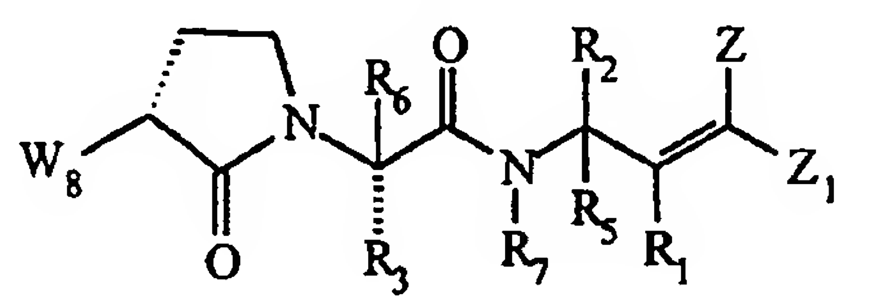
(Ih),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$,

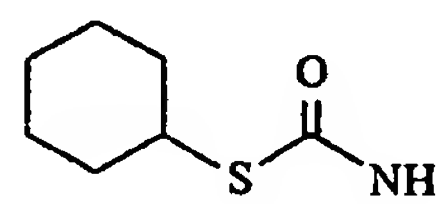
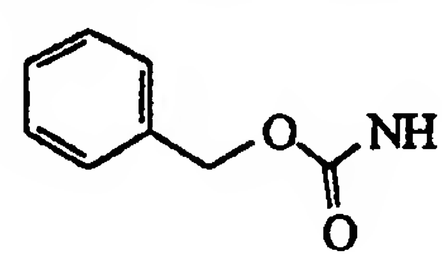
and W_8 is  ,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

27. A compound according to claim 1, having the formula Ij:

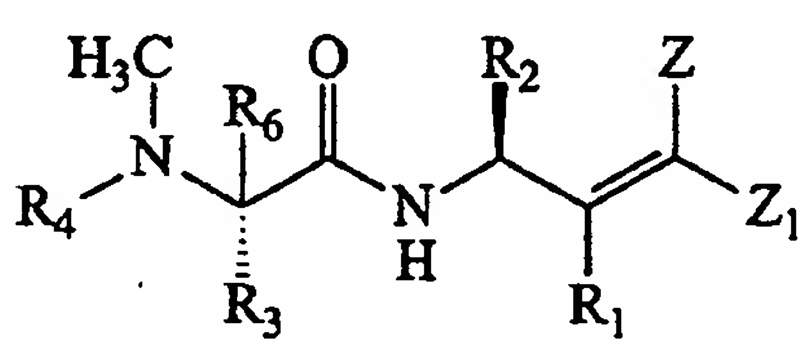


(Ij),

wherein R_1, R_5, R_6, and R_7 are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z is H, Z_1 is $CO_2CH_2CH_3$, and W_8 is  or  ,

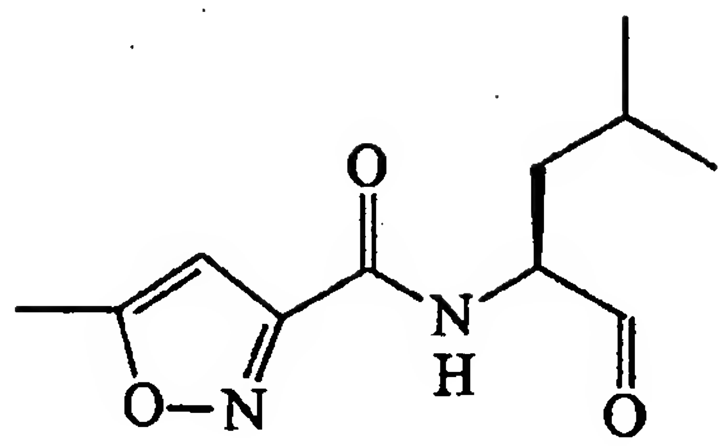
or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

28. A compound according to claim 1, having the following formula X:



(X),

wherein R_1, R_6, and Z are H, R_2 is $CH_2CH_2C(O)NH_2$, R_3 is CH_2Ph, Z_1 is $CO_2CH_2CH_3$, and R_4 is selected from one of the following: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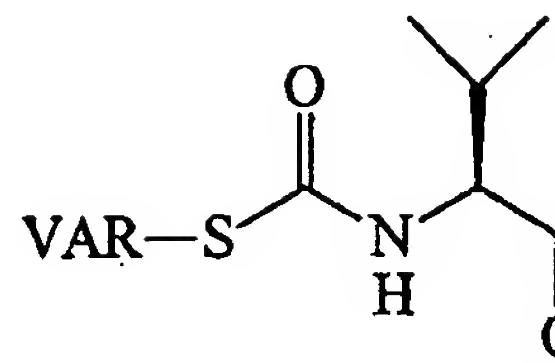
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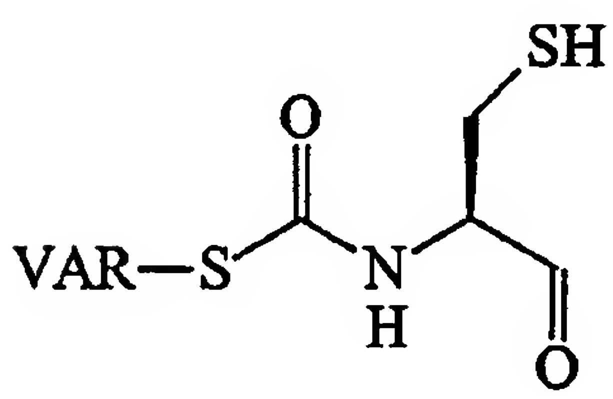
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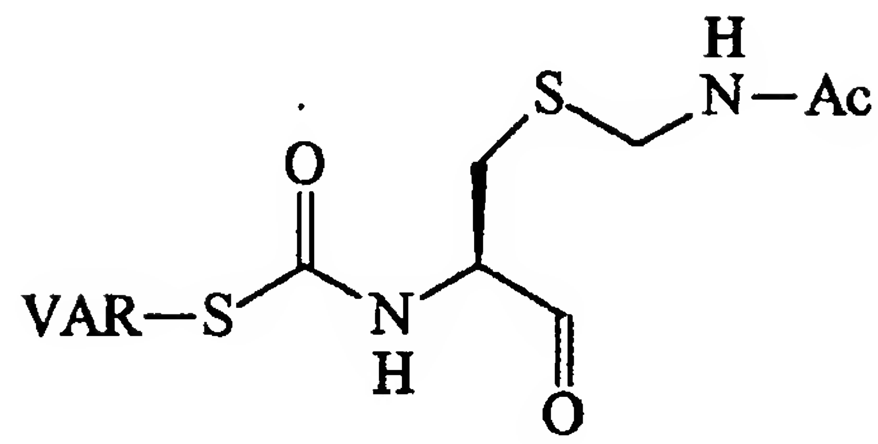
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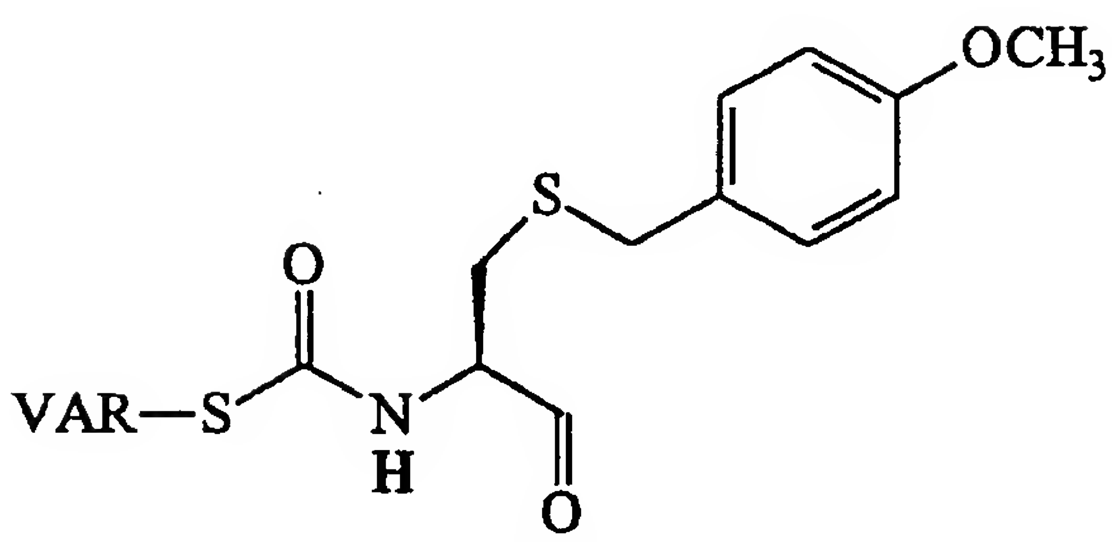
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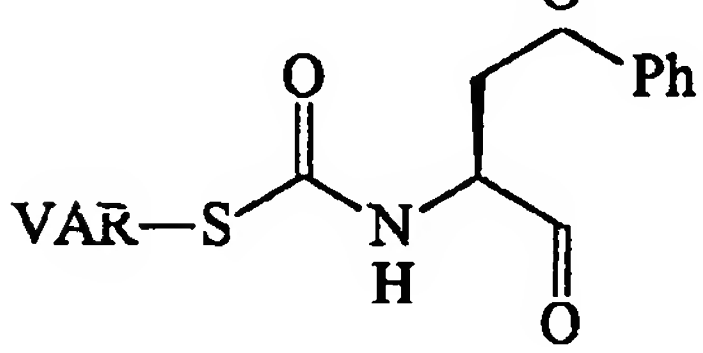
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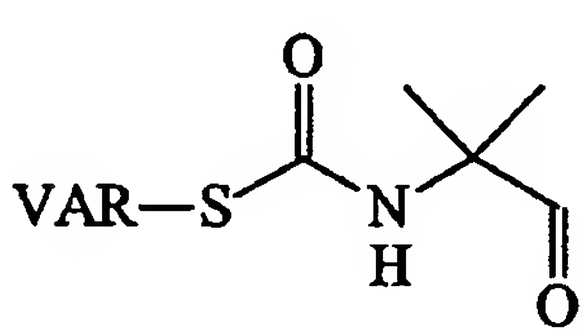
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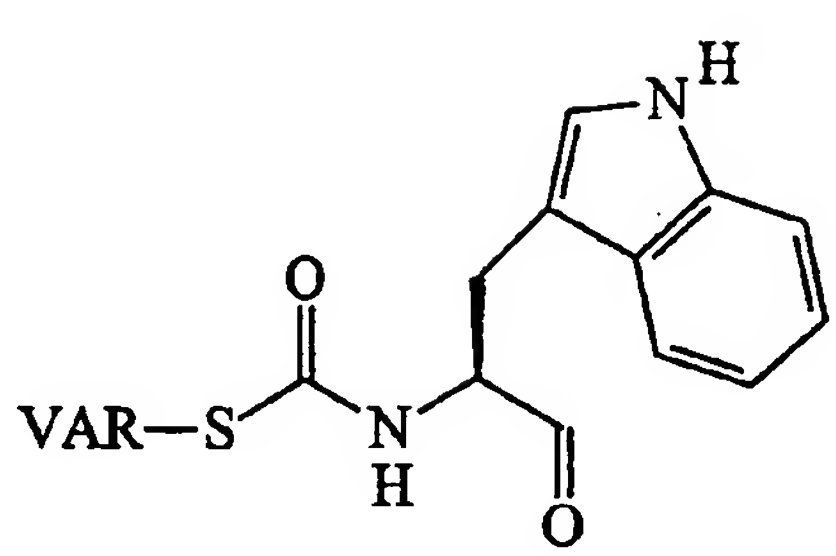
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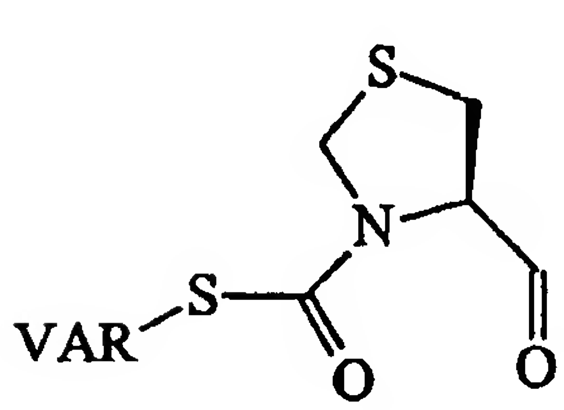
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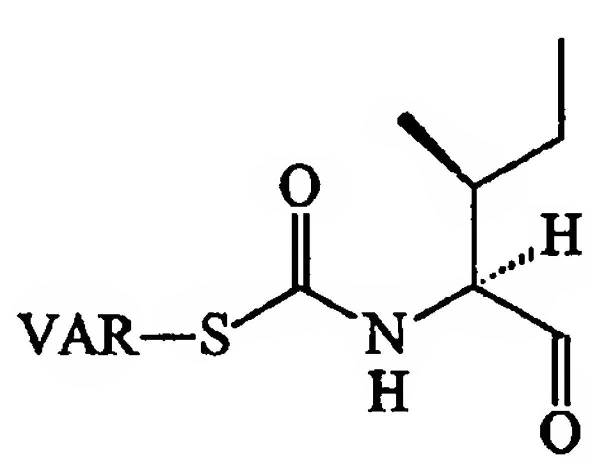
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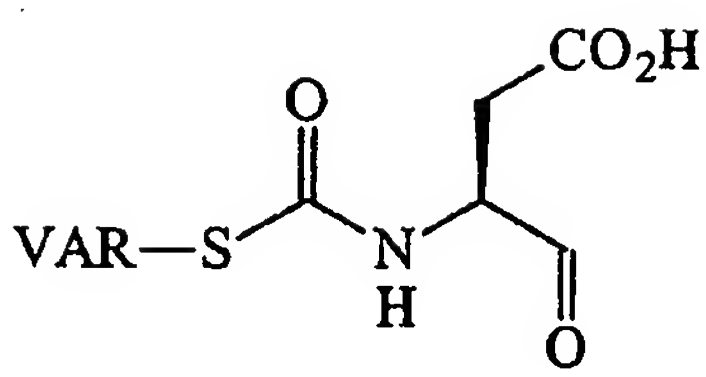
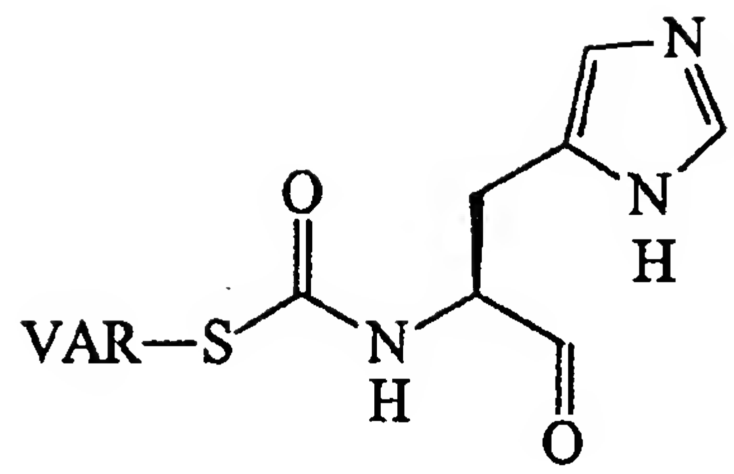
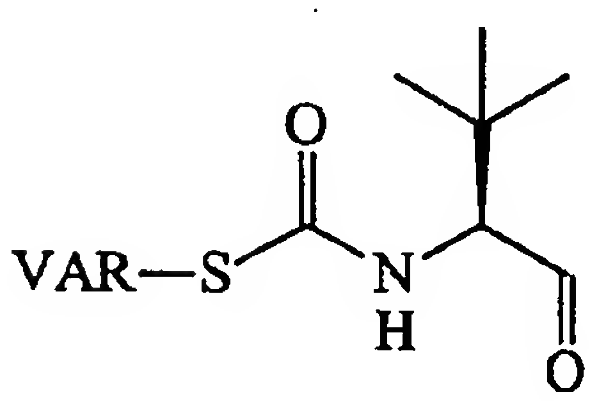
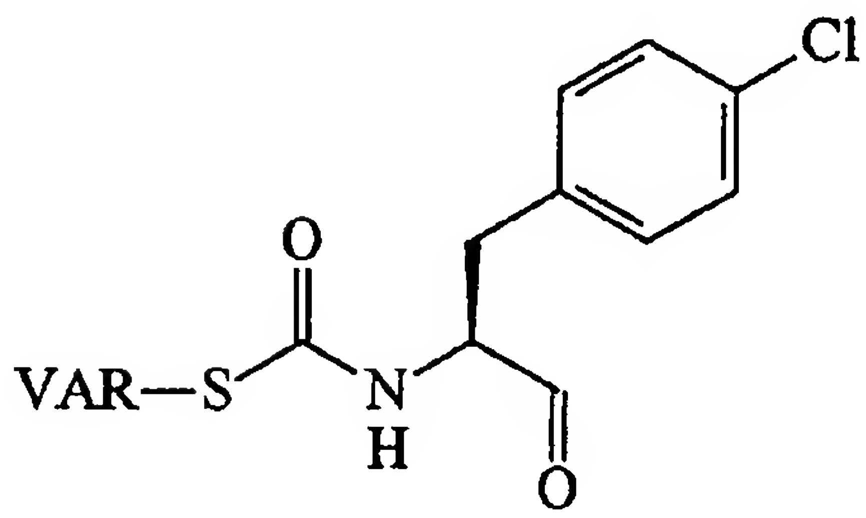
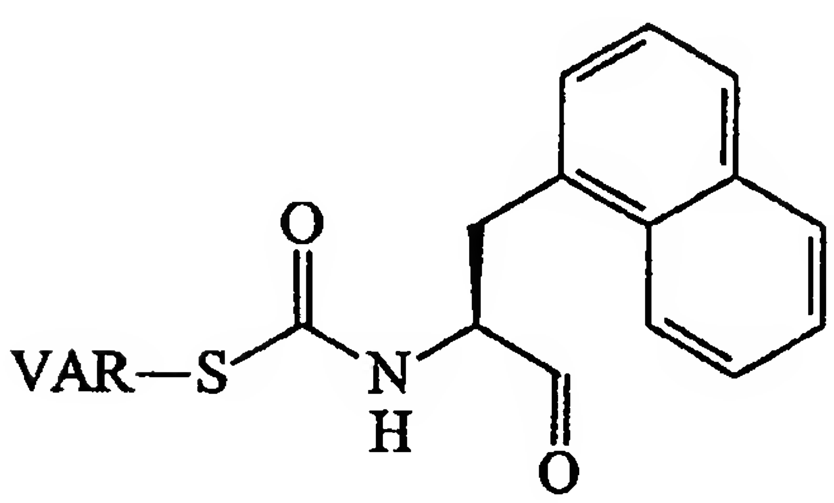
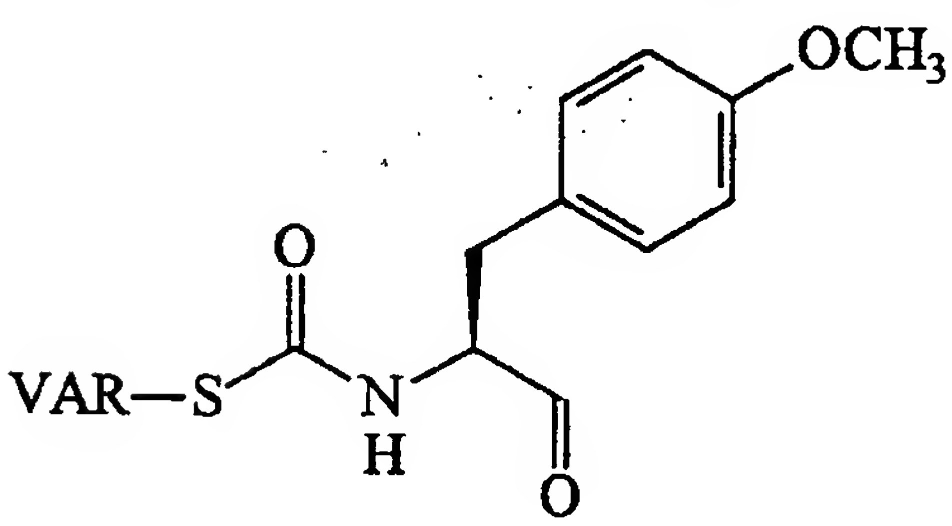
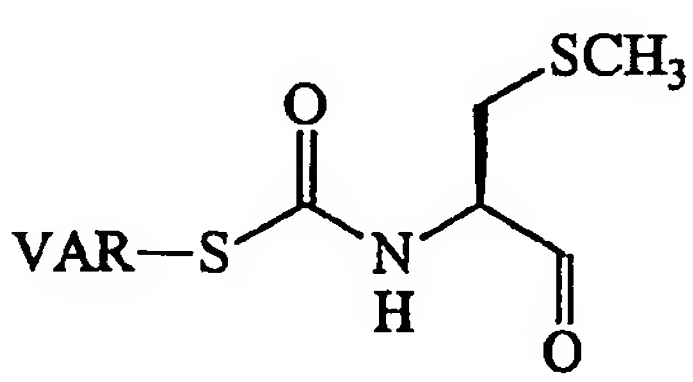
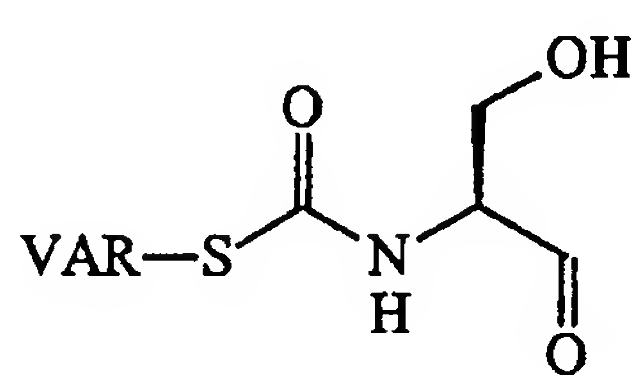
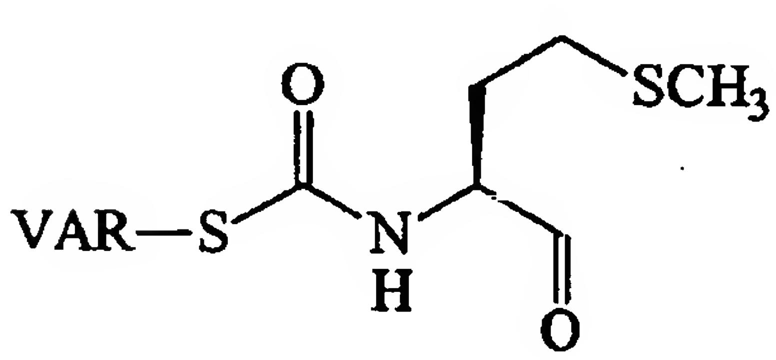
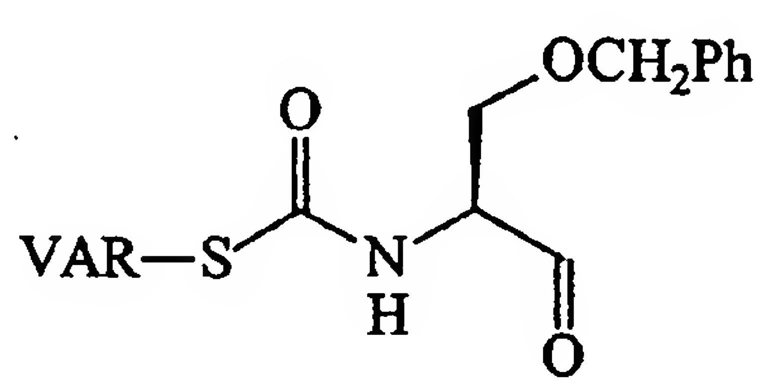
 ;  ;

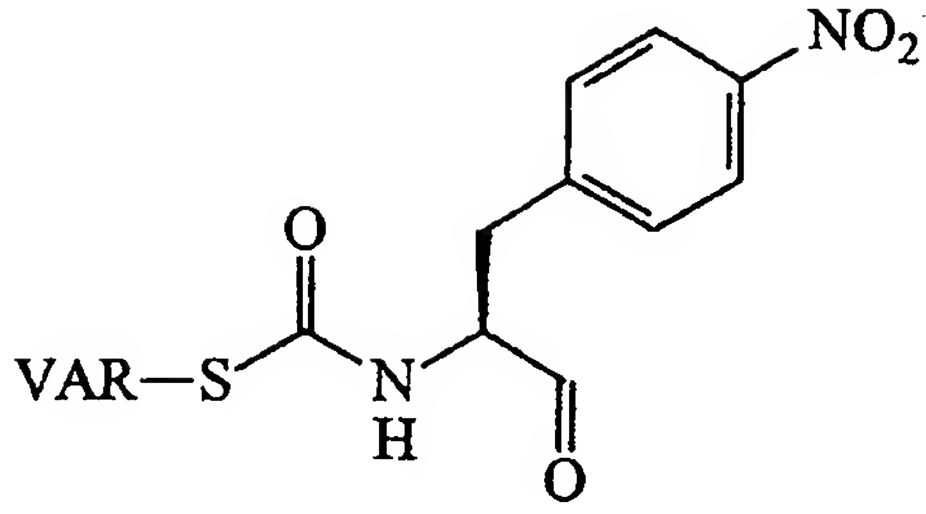
 ;  ;

 ;

 ;

 ;  ;

 ;  ;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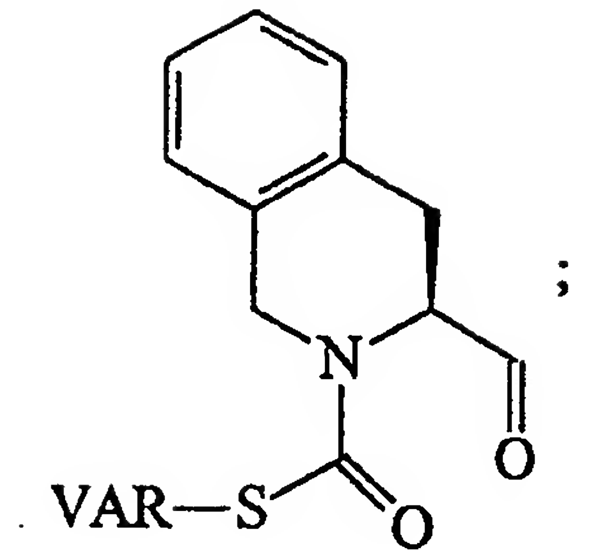
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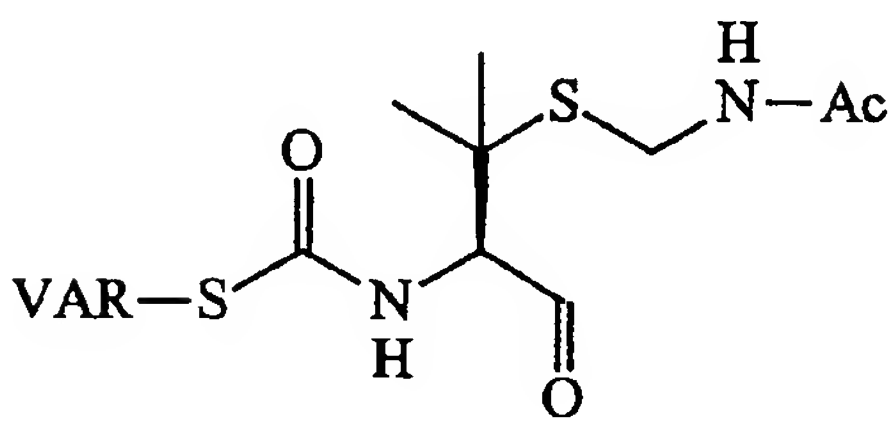
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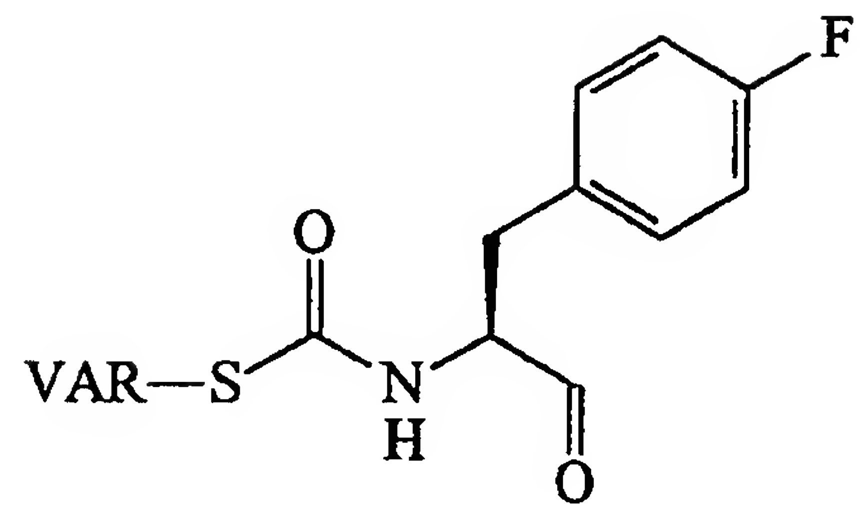
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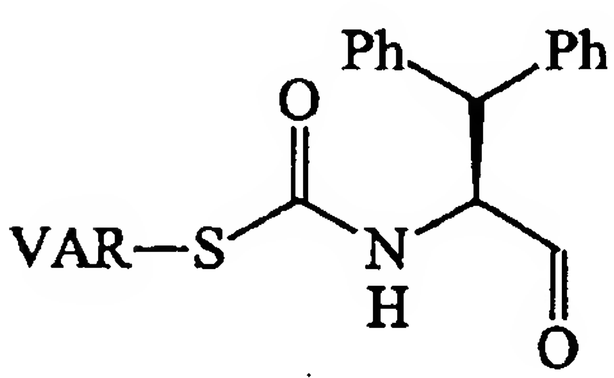
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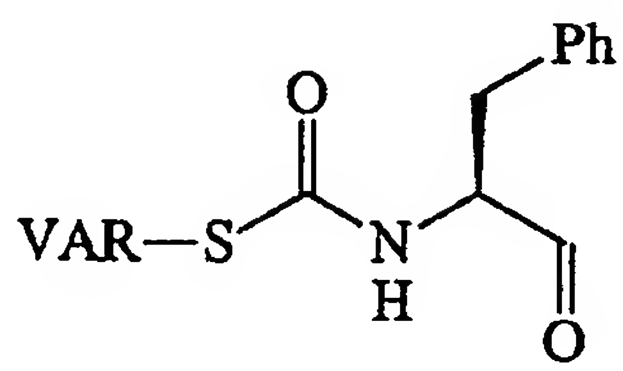
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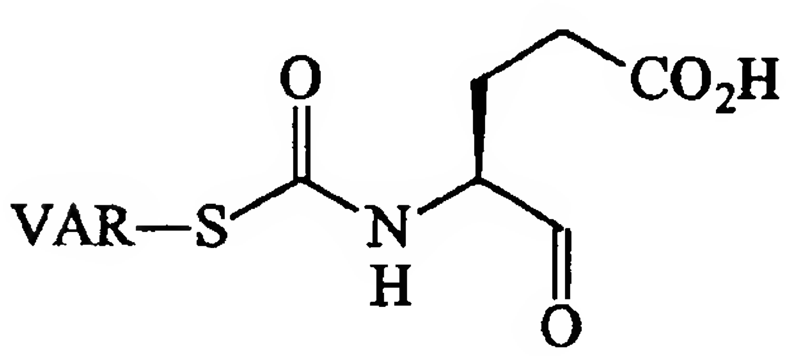
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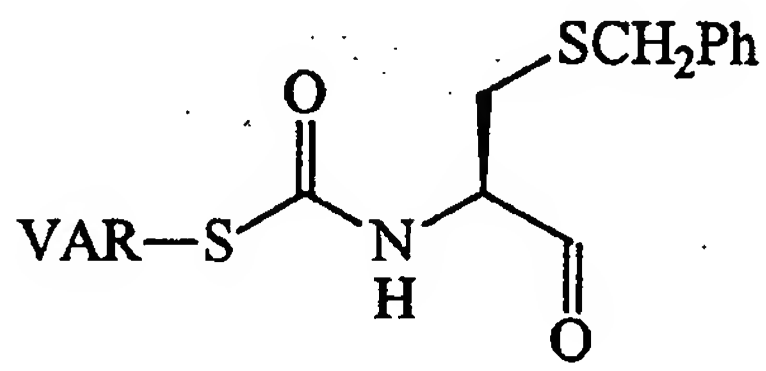
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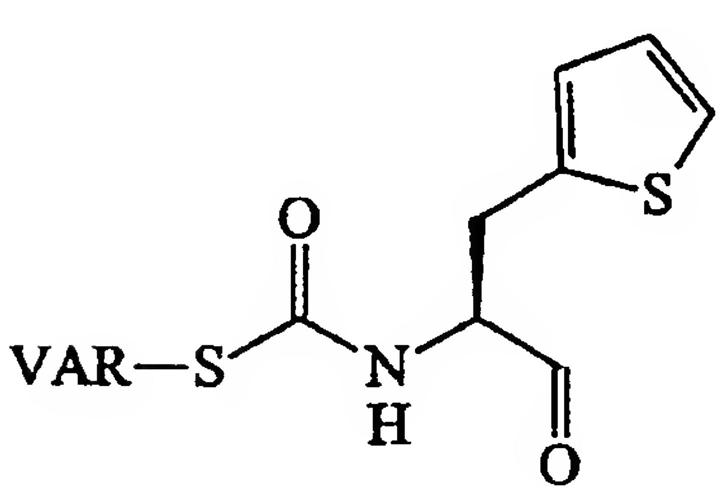
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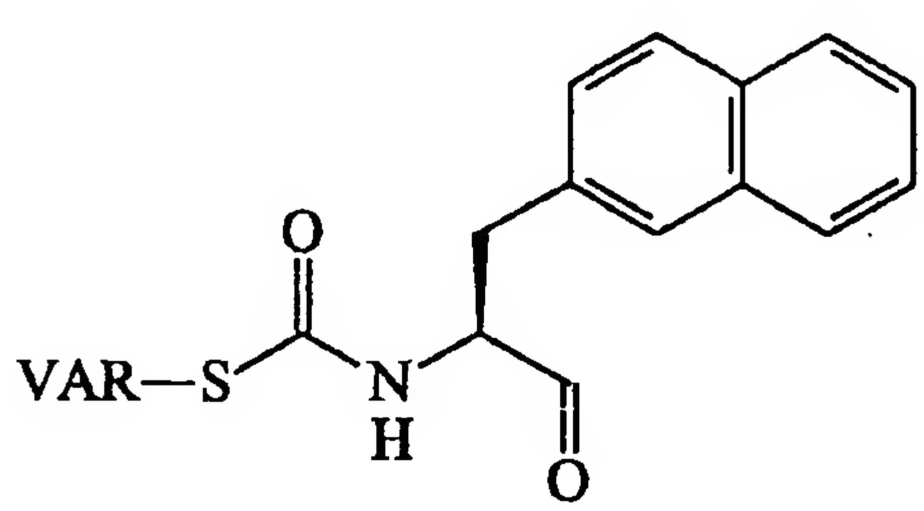
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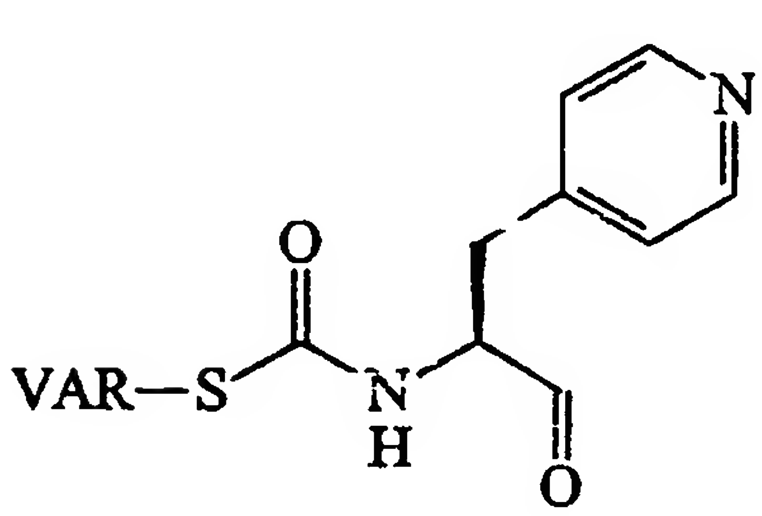
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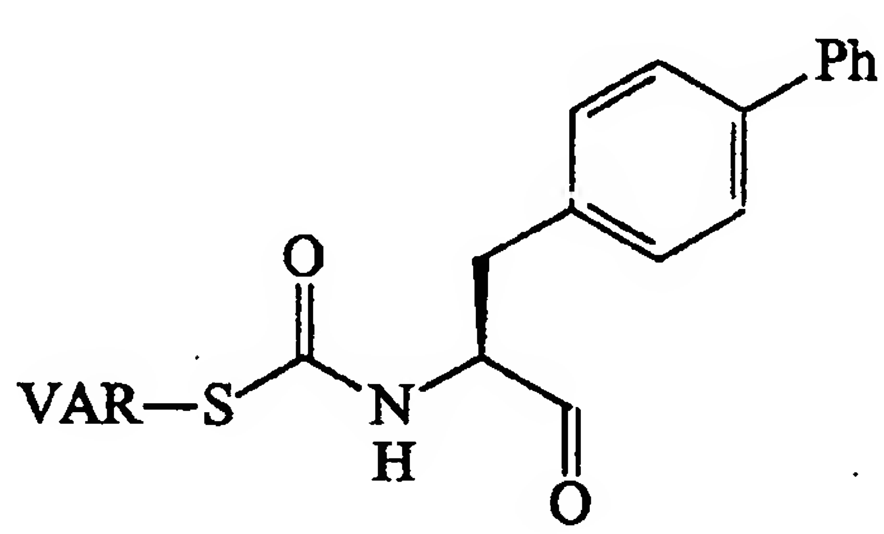
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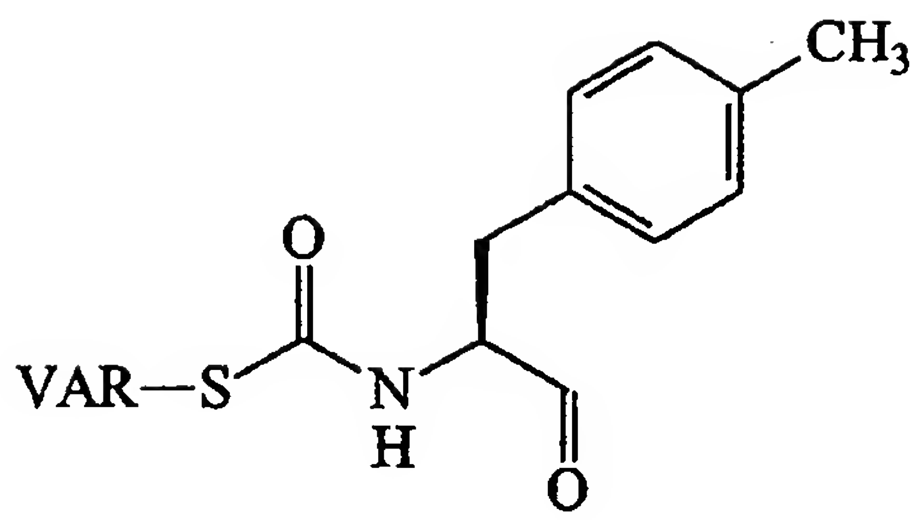
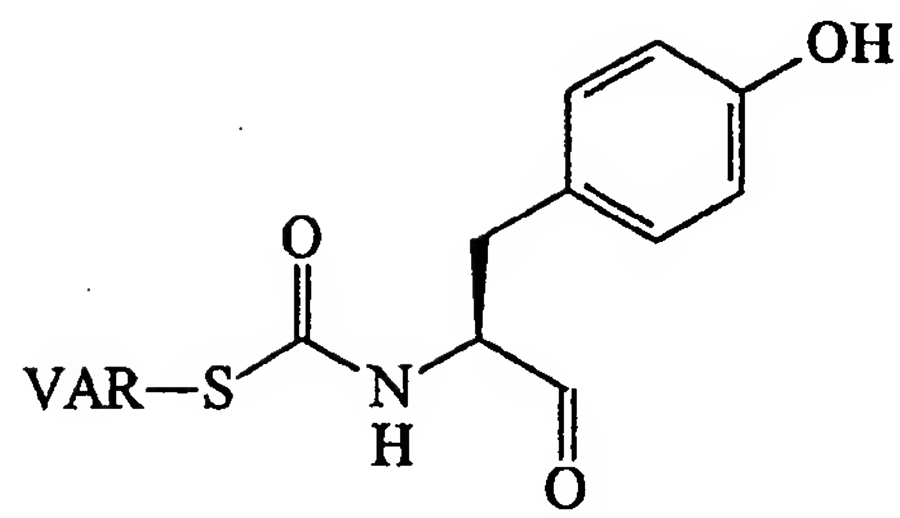
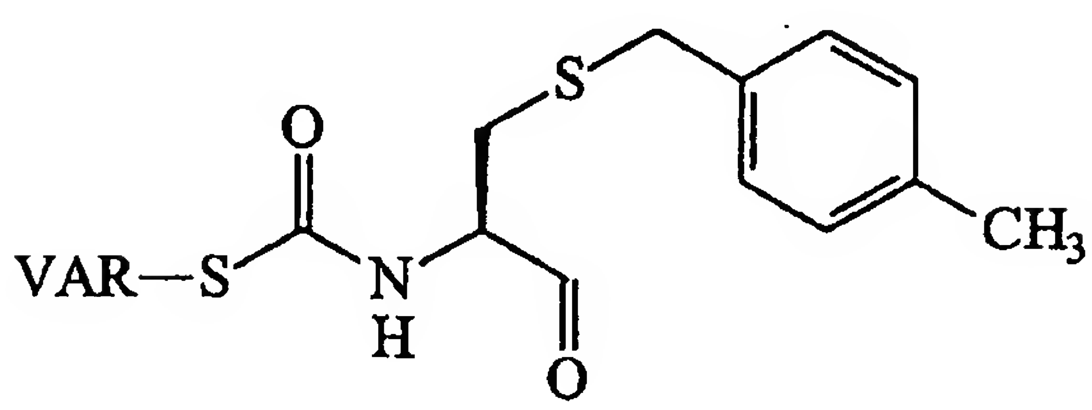
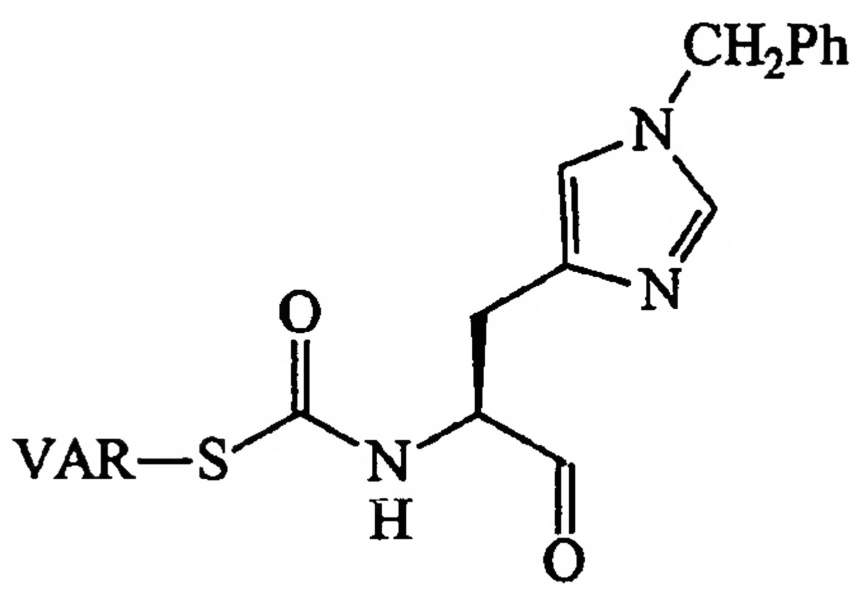
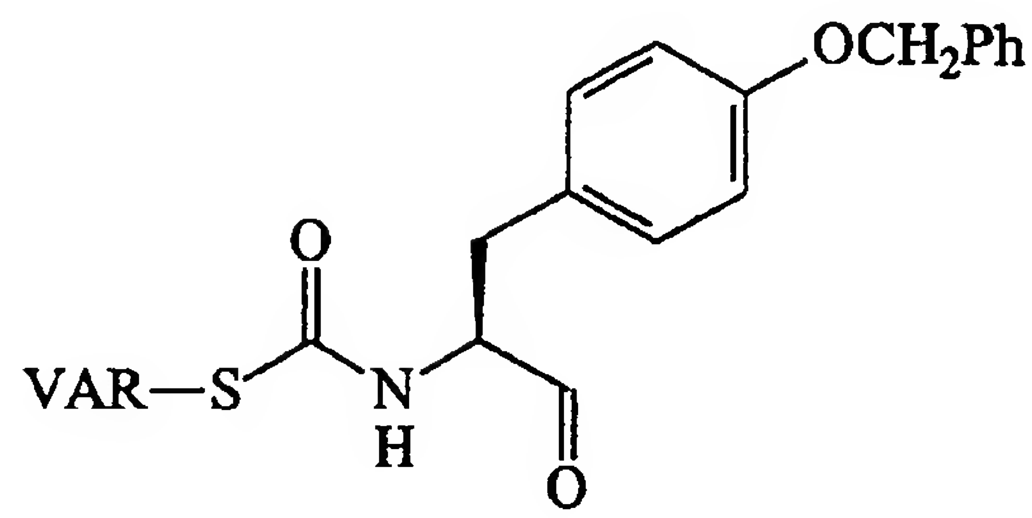
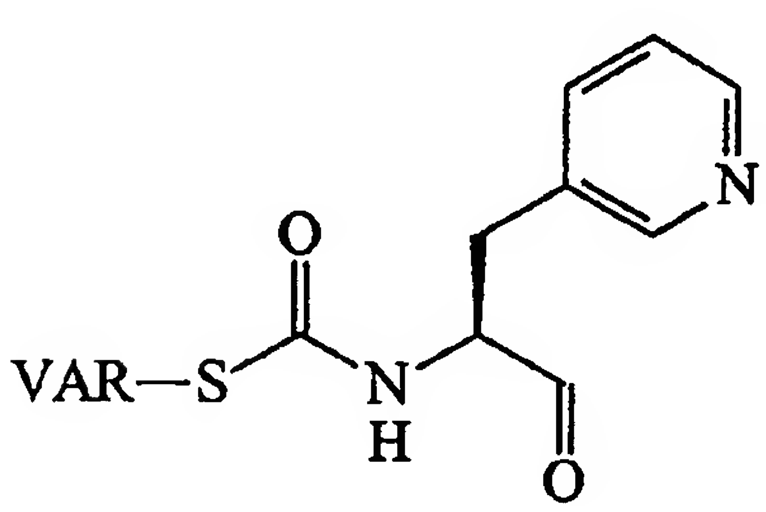
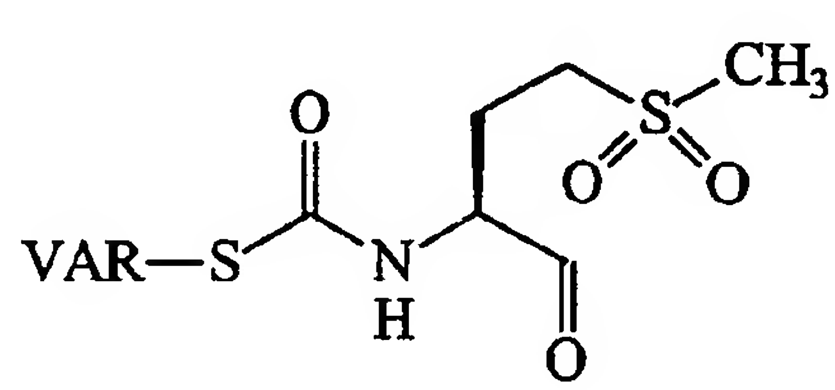
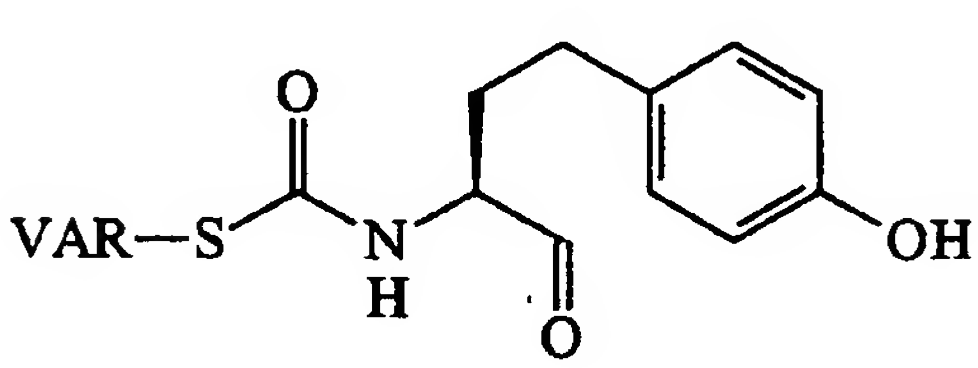
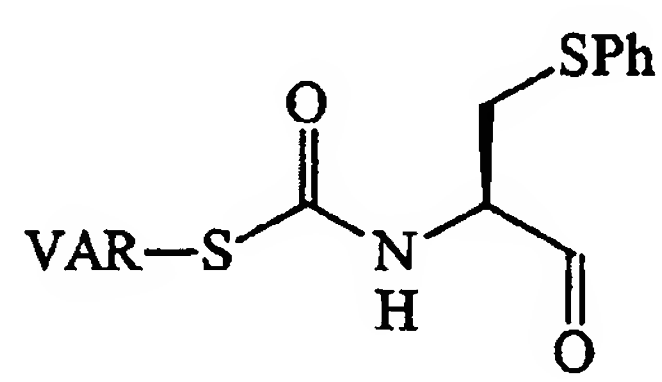
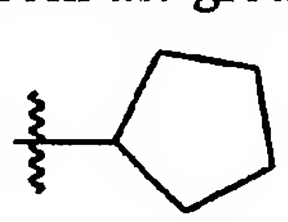
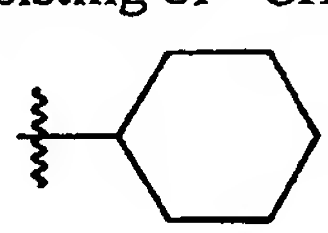
 ;  ;

 ;

 ;  ;

 ;  ;

 ; and  ,

wherein VAR is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2Ph$,  , and  ,

or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

29. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof; and

(b) a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

30. A method of treating a mammalian disease condition mediated by picornaviral protease activity, comprising: administering to a mammal for the purpose of said treating a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

31. A method of inhibiting the activity of a picornaviral 3C protease, comprising: contacting the picornaviral 3C protease for the purpose of said inhibiting with an effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

32. A method of inhibiting the activity of a rhinoviral protease, comprising: contacting the rhinoviral protease for the purpose of said inhibiting with an effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof.

33. A compound according to claim 1, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof, wherein said antipicornaviral activity is antirhinoviral activity.

34. A compound according to claim 1, or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof, wherein said antipicornaviral activity is anticoxsackieviral activity.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/26583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/027 C07C271/22 C07D233/70 A61K38/05 A61K31/415 A61K31/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 43305 A (AGOURON PHARMA) 20 November 1997 see the whole document ---	1-34
P,X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 2. Peptide structure-activity studies." JOURNAL OF MEDICINAL CHEMISTRY, (1998 JUL 16) 41 (15) 2819-34. JOURNAL CODE: JOF. ISSN: 0022-2623., XP002100727 United States see the whole document ---	1-34

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 1999	20/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/26583

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 1. Michael acceptor structure-activity studies." JOURNAL OF MEDICINAL CHEMISTRY, (1998 JUL 16) 41 (15) 2806-18. JOURNAL CODE: JOF. ISSN: 0022-2623., XP002100728 United States see the whole document -----	1-34

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ernational application No.

PCT/US 98/26583

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 30-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ...tional Application No
PCT/US 98/26583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9743305 A	20-11-1997	US 5856530 A	05-01-1999
		AU 3005997 A	05-12-1997
		CA 2254343 A	20-11-1997
		EP 0910572 A	28-04-1999